A Color Atlas of Morphologic Hematology

WITH A GUIDE TO CLINICAL INTERPRETATION

BY

GENEVA A. DALAND, B.S.

CHIEF LABORATORY ASSISTANT IN HEMATOLOGY, THORNDIKE MEMORIAL LABORATORY
RESEARCH LABORATORY TECHNICIAN, BOSTON CITY HOSPITAL

EDITED BY

THOMAS HALE HAM, M.D.

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL
ASSOCIATE DIRECTOR, THORNDIKE MEMORIAL LABORATORY
JUNIOR VISITING PHYSICIAN BOSTON CITY HOSPITAL

ILLUSTRATIONS BY

ETTA PIOTTI

From the Second and Fourth (Harvard) Medical Services and the Thorndike Memorial Laboratory, Boston City Hospital

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FOREWORD

The purpose of this *Atlas* is to furnish a guide for reference in the study of films of peripheral blood stained with Wright's stain The description of the blood, in a variety of clinical conditions, is considered from a diagnostic point of view. The maturation of the blood cells is described and shown in the diagrams and plates so that immature or abnormal forms may be recognized in the peripheral blood or bone marrow. It is emphasized that these diagrams are oversimplified for use as working hypotheses by those who are concerned with diagnosis and treatment No attempt is made to discuss in detail the many theories regarding the origin of the cells or to show, in the diagrams, other possible concepts. The terminology used or the theories of cell origin are not as important as the recognition of the significance of the findings from a diagnostic, prognostic, and therapeutic point of view The morphology of cells of the bone marrow is not discussed separately, since cells of the bone marrow may appear in the peripheral blood in certain physiologic or pathologic conditions The details of quantitative methods, special tests, as well as physiologic and pathologic aspects of the diseases involving red cells, white cells, and platelets are given in *A syllabus of laboratory examinations in clinical diagnosis* [1], (referred to hereafter as the *Syllabus*), which is a companion book of this *Atlas*.

The author is indebted to the late Dr. George R. Minot whose guidance and enthusiasm were enjoyed for many years The constant encouragement, support, and guidance of Dr. William B Castle and Dr. Thomas Hale Ham have made progress in this field possible The author wishes to acknowledge also the assistance and counsel given by Dr Frederic Parker, Jr., and Dr Henry Jackson, Jr, not only in the preparation of this volume, but in the study of the morphology of the blood and the pathology of many unusual cases over many years.

1. VALUE AND LIMITATIONS OF THE BLOOD FILM IN DIAGNOSIS

1. *DETECTION OF ABNORMALITIES OF FORMED ELEMENTS BY BRIEF SCREENING EXAMINATION* A brief but critical screening examination of the blood film stained with Wright's stain is an essential part of the complete examination of each patient Abnormalities of the red cells, the white cells, and the platelets can be detected rapidly by inspection. If abnormalities are apparent, other examinations are indicated, such as red-cell count, determination of the red-cell indices of Wintrobe, reticulocyte count, white-cell count, platelet count, bone-marrow aspirations, and other special tests discussed in the *Syllabus* [1] The variation of the red cells from normal is observed in respect to their size, shape, and hemoglobin content, and the presence of abnormal forms, as discussed in paragraph 5 and shown in Plate I It is usually possible to estimate whether the white-cell count is normal, increased, or decreased An important observation is the deviation from the normal proportion of white cells, as shown by neutrophilia, lymphocytosis, monocytosis, eosinophilia, neutropenia, or lymphopenia The finding of immature cells or of cells not normally seen in the peripheral blood is of great importance Slight variations from the normal in the number of platelets observed in a blood film are of little clinical significance However, the absence of platelets or a definite decrease in their number may indicate a primary or secondary thrombocytopenia The presence of large or abnormal platelets may indicate a fundamental disturbance of the bone marrow

2 *EVALUATION OF THE ACTIVITY OF THE BONE MARROW FROM EXAMINATION OF THE PERIPHERAL BLOOD* The degree of activity of the bone marrow in the production of formed elements may be evident in the film of peripheral blood For example, all the formed elements may be decreased in the peripheral blood, this condition is described by the term pancytopenia The presence of moderate numbers of polychromatophilic macrocytes in a blood film showing normochromic or hypochromic red cells suggests the recent occurrence of blood loss and a physiologic response to the bone marrow. The occurrence of polychromatophilic cells in large numbers in chronic anemia, with icterus, with or without spheroidal red cells, strongly suggests a hemolytic anemia Examination of the blood film is of value in determining the response, or lack of response, of pernicious anemia and the related macrocytic anemias to vitamin B_{12} (liver extract), or of hypochromic iron-deficient anemia to the administration of iron The presence of polychromatophilic cells or, better, the actual number of reticulocytes, indicates the degree of erythropoietic activity of the bone marrow.

3 *CONFIRMATION OF A DIAGNOSIS OR SUPPLEMENTING OTHER DATA* There are many instances in clinical medicine in which data from the blood film aid in confirming a diagnosis or supplement other data available to the physician Thus, the identification of the abnormal cells characteristic of infectious mononucleosis aids materially in distinguishing it from the fatal disease, leukemia Also, the blood film is essential for the establishment of a clinical diagnosis of malaria, Oroya fever, and certain other parasitic diseases Most pyogenic infections are associated with leukocytosis and neutrophilia, whereas leukopenia or neutropenia may occur in such infections as typhoid fever, brucellosis, and virus infections The presence of eosinophilia may suggest a diagnosis of trichinosis

2. PREPARATION OF BLOOD FILMS

A thin, well-stained film of blood is essential for the critical evaluation of the blood cells The blood film should be thin enough so that the red cells do not overlap and the white cells are spread out for observation of details of the nuclear structure, color of the cytoplasm, type of granules, and relative size of the cell

For successful preparation of films of blood, the slides or coverglasses must be washed free from acid and alkali, which alter the staining reaction, and free from grease, which interferes with uniform spreading of the blood film For the most accurate results, the differential count of white cells should be made on a stained film prepared on a coverglass (No 0 or No. 1, ⅞ inch square) In such films, the blood spreads by capillary action and the dispersion of the leukocytes is that of a chance distribution (*Syllabus*, Unit 7, p 82). In slide preparations the distribution of leukocytes is not uniform, since the large red and white cells accumulate in increased numbers along the edge and at the end of the blood film Slide preparations are preferred for the work in parasitology, where a thick drop and a thin film may be prepared on the same slide The use of slides is the method preferred by many for films made from aspirations of bone marrow The reader is referred to the *Syllabus*, Unit 7, for the preparation of solutions,

slides, and coverglasses, and for the technique of making and staining blood films.

1 *SOURCE OF THE SPECIMEN.* It is recommended that capillary blood be used for examination of the formed elements of peripheral blood and that it be obtained by puncturing the lower tip of the lobe of the ear with a No 6 Hagedorn needle with a rather short, beveled blade, or with a No. 11 Bard-Parker blade The instrument should be kept in a $\frac{1}{1000}$ aqueous solution of zephiran containing potassium nitrite as an antirusting agent Obtaining the blood sample from the ear is preferred to obtaining it from the finger, because it causes less pain and discomfort to the patient and is less likely to cause infection In children, it may be simpler to collect the samples from the finger. In infants, the puncture is usually made in the heel. A blood film may be made from venous blood by delivering a very small drop of blood from the tip of the needle on a slide or coverglass The drop is then spread by the use of another slide or coverglass

In an emergency, blood films may be made from samples of venous blood containing anticoagulants, but they are not satisfactory for the morphologic study of white cells, since white cells change in their staining characteristics, develop vacuoles, phagocytose crystals of oxalate, and degenerate gradually on standing. As a result, the nucleus of the lymphocyte may appear to be dividing, the nucleus of the monocyte often appears as a clover leaf, and the lobes of the neutrophil are often separated into distinct parts

2. *PRINCIPLES OF STAINING THE BLOOD FILM* Wright's stain, a common modification of the Romanowsky stain, is a combination of methylene blue, methylene azure, and eosin. As stated by Conn [32], " these compound dyes act on the protoplasm somewhat as follows certain parts of the cell have an affinity for the neutral stain and take it up as such; others, having an affinity for the basic dye, break up the neutral stain so as to obtain the basic portion of it, or if dissociation has taken place, take up the basic ion directly, while other parts of the cell with an affinity for acid dyes similarly combine with the acid portion of the stain " The nucleus of the cells, or especially the chromatin within the nuclei, is assumed to be acid in character (owing largely to the constituent nucleic acid), has an affinity for a basic dye (methylene blue), and is termed basophilic Neutral material is stained violet in color and is termed neutrophilic Basic material is stained by an acid dye (eosin) and is termed eosinophilic. Azurophilic, as the name implies, indicates an affinity for methylene azure, which is red-purple

Brilliant cresyl blue is used as a vital stain to precipitate the basophilic substance of the red cells, which appears polychromatophilic when stained only with Wright's stain The cells containing this precipitated basophilic substance are called reticulocytes Counts may be performed on *fresh preparations or permanent* preparations counterstained with Wright's stain (*Syllabus*, Unit 7, p 55). Whatever method is chosen for a particular study should be used *throughout the investigation* to assure comparable results Prolonged contact of the dye with the cells will give slightly higher values for reticulocytes than a brief exposure. The advantage of the permanent preparation can be readily appreciated, since the counts do not have to be made immediately and the slides may be filed for reference. In reticulocyte preparations the basophilic substance of the white cells is also precipitated in the cytoplasm, so that differentiation of the white cells is sometimes difficult. Such preparations should be used for a differential white-cell count only when plain, Wright's-stained films are not available

3. *EXAMINATION OF THE QUALITY OF THE STAINED BLOOD FILM.* A general survey of the blood film should be made, using the high dry objective of the microscope, to judge the quality of the film In most fields examined, the red cells and white cells should be clearly separated, should show no artifacts such as vacuoles in the red cells, and should not show significant amounts of precipitate The staining should be uniform throughout The stain should be alkaline enough to stain clearly the platelets, polychromatophilic cells, granules in the neutrophilic series, stippled cells, and the nuclei of the cells, it should be acid enough to bring out the contrast between the nuclei and the cytoplasm of neutrophils

The optimum pH is about 6 7 – 6 8 for the buffer solu- [illegible] on the film Ex-

ing, coverglasses that were not thoroughly rinsed, or areas that were still moist when the coverglass was mounted Excessive blue staining may be due to alkali, to excessive thickness of the film, or to evaporation of the alcoholic stain and drying of the film. In thick films, when the red cells are piled up, the cytoplasm of the white cells will be condensed about the nucleus so that structure cannot be observed and the granules are not distinct enough to be identified

The distribution of the cells should be uniform, without a concentration of cells at one end or around the periphery This condition is difficult to obtain in the slide preparation Precipitate on the film interferes with the recognition of platelets and reticulocytes and may be avoided by floating off the precipitate formed in staining, by thorough washing of the films, and by filtering the stain frequently The presence of small bubblelike deformities of the surface of the red cells is an artifact

indicating that the film was mounted before being thoroughly dried. The mounting medium, preferably methacrylate, should spread beneath the entire film, since air pockets interfere with clear definition of the cells. If the stained blood film is unsatisfactory, it is a waste of time to examine it in detail, since the results are unreliable and may be seriously misleading. Another blood film should be prepared The effects of these technical variations on the results of quantitative evaluation of the cells are discussed in the *Syllabus*, Unit 7.

3. PREPARATION OF THE COLOR PLATES

1 *USE OF WRIGHT'S STAIN IN THIS ATLAS.* The films of peripheral blood reproduced in this *Color atlas* were stained with Wright's stain Although this is a limited method of study, it is of practical value, since Wright's stain is widely used in clinical medicine. Accordingly, the color values and descriptions in this book are limited to those obtained by using Wright's stain and brilliant cresyl blue. The structure of the cells as described results in part from fixation by methyl alcohol contained in Wright's stain The color of the stained cells is an expression of the affinity of the cellular elements for the acid, basic, or neutral portions of this stain. Other methods of staining, such as supravital staining, the peroxidase stain, and histochemical methods, are of value in special instances (*Syllabus*, Unit 7, pp. 67 to 72).

2 *PREPARATION AND USE OF THE COLOR PLATES* The cells in the color plates (Plates I to XIV) were drawn using a camera lucida and painted in water color as they were observed through the microscope with a magnification of 1200. Each plate represents a composite of two or three oil-immersion fields from blood films of patients with proved diagnoses In these plates will be found the cells that occur in peripheral blood in the normal subject, as well as most of the progenitors of blood cells The immature forms that normally are found in bone marrow or other tissues may occur in the peripheral blood in abnormal states. Thus, the identification of cells in these plates of peripheral blood will aid in performing differential cell counts of aspirations of bone marrow. The plates are limited in number and represent conditions in which the film of blood is of definite diagnostic value. Emphasis is placed on the interpretation of the cells found in these films and on the differential diagnosis of the conditions in which related abnormalities may be found.

4. GENERAL CHARACTERISTICS OF FORMED ELEMENTS OF BLOOD STAINED WITH WRIGHT'S STAIN

1 *CHARACTERISTICS OF THE CELL* The formed elements of the blood include the nucleated red cells and white cells, the nonnucleated mature red cells, and the platelets The cytoplasm, enclosed in cell membrane, may appear clear or may contain granules rods, or foreign particles that have been phagocytosed The nucleus of white cells and of nucleated red cells contains a network of chromatin material, and, in the primitive cells, one or more nucleoli may be present within the nucleus With Wright's stain, the nucleolus appears as a circumscribed area, about 2 to 3 μ in diameter, that is less densely stained than the surrounding nucleus In films stained with brilliant cresyl blue, the nucleolus appears as a light-blue area Nucleoli should be distinguished from dark-staining clumps of chromatin and from vacuoles which may appear as clear colorless areas of variable size and number in either the nucleus or the cytoplasm of the cell Films that have been stored for years sometimes show degenerative changes or clear areas in the nuclear chromatin that are not nucleoli In films of bone-marrow aspirations or in the peripheral blood in the leukemias, nuclear division or mitosis may be seen

2. *IDENTIFICATION OF CELLS* For study and identification of the cells in a film of blood it is essential to examine the preparation with oil-immersion magnification (1000 to 1200) and adequate illumination It is necessary not only to see the cells but to " see the inside of the cells," to study the color of the granules and the details of the structure of the nucleus The variation in types of blood cells is great. Cells may be identified as belonging to the red-cell series, the white-cell series, or the thrombocytic series. Further classification of the white cells may be made by grouping them into the granulocytic, lymphocytic, monocytic, plasmacytic, or histiocytic series To understand the different cells in each series, the several stages of development of the cell must be appreciated (see Figs 4, 5, 6, 7, 8) These stages [illegible]

cells seen in the peripheral blood is a rough index of the physiologic response of the bone marrow or other tissues, or may indicate abnormal growth as in neoplastic diseases The appearance of abortive types of cells is also a sign of abnormality that may have a serious prog-

nosis Such cells may be present in a terminal illness, in overwhelming sepsis, or after prolonged irradiation

An accurate report of the blood findings on the part of the technician is important. An understanding of these abnormal cells and their significance is equally important for the physician, in order that he may interpret the physiologic and pathologic significance of the laboratory data

If a cell is difficult to classify, it should be compared with cells that can be recognized for the structure of the nucleus, the color and structure of the cytoplasm, and the type and color of the granules If a cell cannot be recognized as belonging to any of the established series, it should be recorded as an abnormal cell and described in detail, with a drawing

Cell development can be described in a systematic manner, since the morphologic changes are similar in some respects for each series of cells described here. Some generalizations will be helpful in studying the cells, although there are many exceptions to all the rules that can be established Differentiation of the type and age of the cells must be determined by a consideration of many factors. Some of these factors are size, structure of the nucleus, color of nuclear chromatin, presence of nucleoli, character and color of the cytoplasm, relative proportion of nucleus and cytoplasm, granulation, and color of the granules No one factor can be considered alone, although the structure of the nucleus is probably the most valuable single guide.

(*a*) Relative Size of Cells In general, immature cells are larger than mature cells The stem cell is definitely larger than the other blasts of any series (Figs 1, 4, 5, 6, 7, and 9). Other examples may be seen by comparing the proerythroblast with the normoblast, the polychromatophilic cell with the mature red cell (Fig 1), and the myelocyte with the mature granulocyte (Fig. 4). Abnormal eosinophils in infectious states are usually larger than the normal eosinophil In infections the myelocytes and band forms are larger than the neutrophils, and the neutrophils may be larger than those in normal blood The mature small lymphocyte is the smallest cell of the white-cell series The plasmablast and the young plasma cell are larger than the mature plasma cell, although the mature cell may be larger in the leukemic states.

(*b*) Relative Size of Nucleus and Cytoplasm. The nucleus in the immature cell takes up a larger proportion of the cell than it does in the mature cell Examples of this are especially striking in the granulocytic series (Fig 4) In the lymphocytic series (Fig 5) this generalization holds except for the small lymphocyte, in which the nucleus occupies most of the cell

(*c*) Nuclear Structure as a Distinguishing Characteristic The characteristics of the nuclear structure are illustrated diagrammatically in Figs. 1, 4, 5, 6, 7, 8, 9 and in more exact detail in the color plates (I through XIV). These details are realized most effectively if the observer reproduces the cells on paper either with pencil or with colored crayons.

In general, the young cells have a uniformly granular structure of the chromatin of the nucleus, while the mature forms of each series are characterized by a heavy condensation of chromatin, as is seen in the small lymphocyte, plasma cell, neutrophil, and normoblast However, the monocyte and histiocyte are definitely exceptions to this generalization The color of the nuclei of the mature cells in general is blue-purple, and is more intense than the red-purple of the blast nuclei. Nucleoli are present in the youngest forms It is of utmost importance to differentiate the blast from other cells by careful observation of the type of the nucleus. The series to which a blast cell belongs is determined in part by the size of the cell, the color of the cytoplasm, and the structure of the nucleus as compared with other blasts, and in part by the presence of other cells of the same series (by the "company they keep"). Blasts from more than one series may be present, as, for example, granulocytic and erythrocytic series See also pp 25, 36–38, 42–44, 45–47, 51–56.

(*d*) Color of the Cytoplasm as a Differential Criterion The stem cell, the proerythroblast, and all the blasts of the white-cell series are characterized by the deep basophilia of the cytoplasm, although the shade and character of this deep blue varies somewhat in the different series. The proerythroblast has a gray-blue cytoplasm, somewhat similar to that of the monoblast. The cytoplasm of the myeloblast is usually rather a clear deep blue, but is more abundant than that of the lymphoblast.

The change from the deep basophilia of the proerythroblast to the hemoglobin-containing cytoplasm of the normoblast and the mature erythrocyte may be seen diagrammatically in Fig 1 and in Plate I In the intermediate stages both elements — the basophilic substance and the hemoglobin — are factors in producing the polychromatophilia of the cytoplasm, the relative amount of each substance determining the intensity of the color. As the cell matures, the basophilic substance decreases and the hemoglobin increases

The disappearance of the basophilic substance as the cell matures is illustrated in the granulocytic series by comparison of the cytoplasm of myelocyte A with that of myelocyte C (Plate X).

In the lymphocytic series the mature small lymphocyte and the large lymphocyte have the lightest-blue ... young

... as the

... deep-

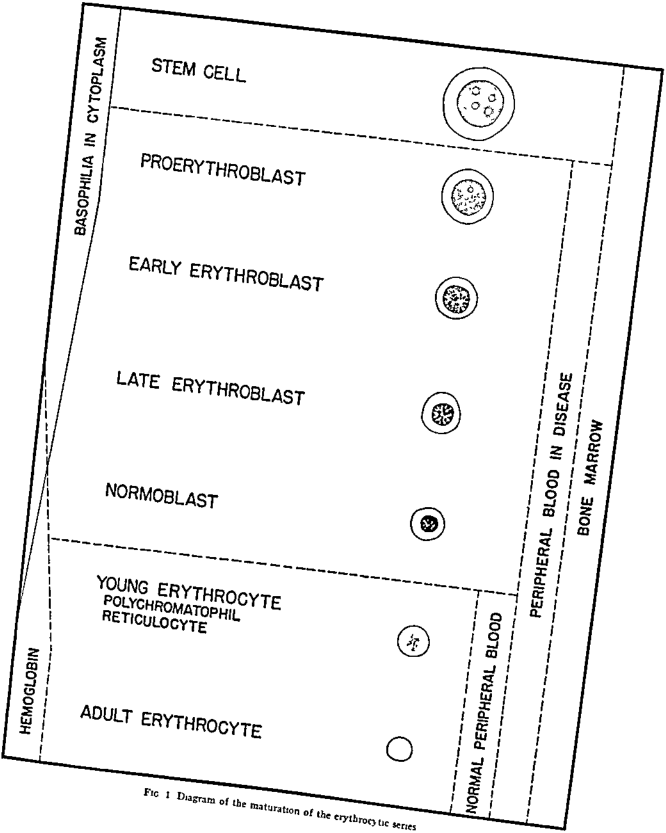


FIG 1 Diagram of the maturation of the erythrocytic series

blue cytoplasm, which may be due to a crowded area in the film with resulting condensation of the cytoplasm about the nucleus, or they may be young forms, according to the studies of Wiseman [188]. If the films are thick, it is difficult to tell the lymphocyte from the monocyte because the details of the cytoplasm cannot be seen. The mature plasma cell has a gray-green-blue cytoplasm which is usually less intense than the blast of the same series.

(*e*) COLOR VALUES Use of the compound, polychromatic, Romanowsky stains, such as Wright's stain [*32*], affords the advantage of staining the acidophilic and basophilic elements at the same time This actually means that there is a gradation of staining reaction from the deep blue (acid in reaction but "basophilic" in staining) of the cytoplasm of the blast to the red (basic in reaction but "acidophilic" in staining) of the mature red cell This gradation in color value applies to the nucleus, to the cytoplasm, and to the granules and may be more clearly understood from the systematic color scheme shown in Fig 2 In this chart the color relations of the cellular elements of the blood (nucleus, cytoplasm, and granules) are shown graphically in a color circle Practically all of the colors developed in the cells by the Wright's stain are within one sector of this circle or between the blue and the red. This produces a harmony in the colors of the stained blood cells that is pleasing to the eye It also shows why it is difficult to describe the delicate changes and slight differences in color. The chart expresses only color value; the intensity of color (pink to red, or light blue to deep blue) is not indicated The points indicated in the center and on the periphery of the circle are the colors at their fullest intensity. The primary colors are indicated by the solid lines and the secondary colors by the broken lines.

5. THE RED CELLS AND THE ERYTHROCYTIC SERIES (Fig. 1)

1 *TERMINOLOGY OF THE NUCLEATED FORMS OF THE ERYTHROCYTIC SERIES* Before a study of abnormal bloods can be undertaken, the description and terminology of the normal and abnormal forms of red cells must be understood In the description of the nucleated forms, the characteristics of the nuclear chromatin serve as criteria for classification, since the size of the cell and the color of the cytoplasm are so variable.

All investigators are agreed that the nucleated red cells seen in the blood and in the bone-marrow aspirations in pernicious anemia are abnormally large and that the bone marrow shows an increase in proportion of cells with deeply basophilic cytoplasm These cells are called "megaloblasts" by many authors Many of these cells are strikingly atypical, showing clumped or reticular structure of the nucleus, while the cytoplasm is still deeply basophilic Normally, this type of nuclear structure occurs with a more mature cell, as evidenced by cytoplasm that is less basophilic There is no evidence that these cells have an origin different from that of normal red cells, although their maturation is abnormal Davidson, Castle, and their associates [47] have shown, in patients with pernicious anemia, that the abnormal "megaloblastic" red cells disappear from the bone marrow when anoxia is relieved by transfusion of the patient before any treatment with vitamin B_{12}

Many different names have been applied to the cells of the erythrocytic series The following list gives the names used in this *Atlas*, in italics, together with the terms employed by other authors. — *stem cell* haemoblast [137], lymphoidocyte [68, 137], hemocytoblast [36, 98, 116, 183], erythrogone [46]; *procrythroblast* [35, 68, 98, 111, 137, 168]: megaloblast [53, 80, 90, 141], normoblast A [46], pronormoblast [36, 55, 103, 186], rubriblast [31]; *early erythroblast* [35, 53, 80, 141]: erythroblast [90], basophilic erythroblast [35, 68, 116, 168], basophilic normoblast [36, 55, 103, 111, 186], early normoblast [98, 183], prorubricyte [31], normoblast B [46]; *late erythroblast* [35, 53, 80]: polychromatic erythroblast [35, 68, 116, 168], polychromatic normoblast [36, 55, 103, 111, 186], pronormoblast [90], intermediate normoblast [98, 183]; *normoblast* [35, 53, 80, 90, 141]: acidophilic erythroblast [35], eosinophilic: erythroblast [168], orthochromatic erythroblast [68, 137], orthochromatic normoblast [55, 103, 186], pyknotic normoblast [36], late normoblast [98, 183], normoblast C [46], metarubricyte [31]; *young erythrocyte (reticulocyte* or *polychromatophil), adult erythrocyte:* rubricyte [31].

2 *DESCRIPTION OF NORMAL AND ABNORMAL CELLS OF ERYTHROCYTIC SERIES (PLATE I)* The cells are described in order from the mature erythrocyte to the least mature form, the proerythroblast The figures in italics refer to the cells shown in the plate.

(*a*) ERYTHROCYTE (mature red cell, *1*). The diameter of the normal red cell is between 5 and 9 μ with a mean of 7.2 to 7 8 μ in normal individuals The diameter of the abnormal red cell may vary from 2 to 14 μ. The color of the cell is a yellow-red, owing to staining of hemoglobin The pale central area results

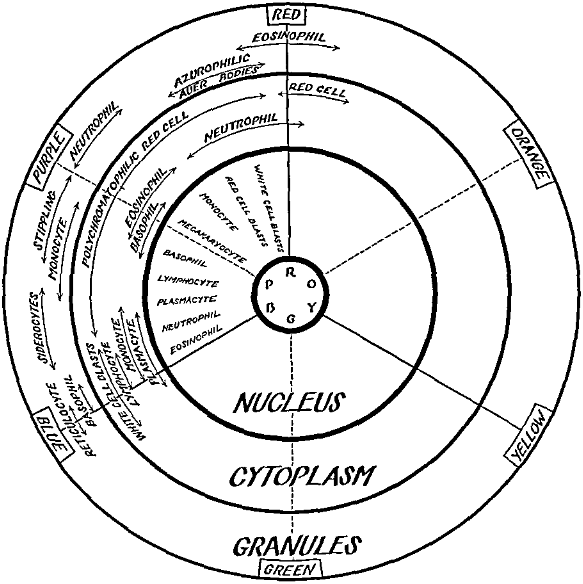


FIG 2 Graphic representation of the color values of the nucleus, cytoplasm and granules of blood cells stained with Wright's stain

from the thinness of the layer of hemoglobin due to the biconcave shape of the normal red cell No nucleus or granules are present in the normal red cell.

(*b*) POLYCHROMATOPHILIC ERYTHROCYTE (immature red cell, *2*). This cell is usually larger than the adult cell of the same blood sample. The polychromatophilia is evidenced by the blue-purple color of the cell No nucleus or granules are normally present, but nucleated red cells may also show polychromasia of the cytoplasm.

Reticulocyte (immature red cell, *7a*, *7b*, *7c*). This cell is the same stage as the polychromatophilic erythrocyte but is vitally stained with brilliant cresyl blue (p. *2*) so that it can be recognized and counted more easily than polychromatophilic cells The basophilic material in the cell is precipitated by the cresyl blue as a heavy network of blue substance in the younger forms (*7a*), a moderate amount in the intermediate forms (*7b*), or fine scattered reticulum in the older forms (*7c*). Accordingly, there is a quantitative relation between the amount of reticulum in the cell and the age of the cell [87]. There should be no polychromatophilic cells remaining in a film stained for reticulocytes, since all of the diffuse polychromatophilic material should appear as precipitated reticulum

(*c*) NORMOBLAST (*3*) The normoblast may vary in diameter from a normal range of 6 or 7 μ up to 12 to 14 μ in pernicious anemia The cytoplasm may be acidophilic or polychromatophilic. The nucleus is a small, condensed mass of chromatin, usually deep purple Very little structure is evident in this compact nucleus In pathologic conditions the nucleus may be divided into two, three, or more portions (*3b*). In the blood film stained with brilliant cresyl blue, reticulum may be very dense (*3a*) in cells that would show marked polychromatophilia with Wright's stain alone

(*d*) LATE ERYTHROBLAST (*4*) The erythroblast is larger than the erythrocyte or normoblast The nuclear chromatin is broken up into segments, sometimes radially arranged like the spokes of a wheel The cytoplasm at this stage is usually polychromatophilic For this reason this cell is termed "polychromatophilic erythroblast" by some hematologists

(*e*) EARLY ERYTHROBLAST (*5*) The chromatin of the nucleus of the early erythroblast is broken up into fine clumps It is not as granular as in the proerythroblast, but is more finely divided than in the late erythroblast. The cytoplasm is basophilic.

(*f*) PROERYTHROBLAST (*6*) The proerythroblast is the youngest form of the erythrocytic series that can be distinguished from the blasts of the white-cell series It is usually larger than the normoblast or erythroblast The cytoplasm is a deep blue (basophilic) with a little more purple than in the other blasts The nucleus is made up of fine uniformly granular chromatin, is purple in color, and is definitely round in shape Nucleoli are usually present.

(*g*) STEM CELL. The stem cell is larger than any other blast form (see Plate XIII, *8*). The finely granular, purple nucleus is less intense in color than the deeply basophilic cytoplasm More than one nucleolus may be present in this primitive cell The stem cell may be seen in the peripheral blood in leukemia in association with other blast forms, or in stem-cell leukemia in which the type of cell is primitive and its series cannot be identified.

(*h*) ABNORMAL NUCLEATED RED CELLS. The nucleus of the normoblasts may appear single (*3*), double, or multiple (*3b*) Often normoblasts or erythroblasts are seen with a nucleus showing division or disintegration.

The large abnormal forms with reticular nuclei and deeply basophilic cytoplasm, which are characteristic of the bone marrow in pernicious anemia, may be seen in the blood The dyssynchronism of maturation of nucleus and cytoplasm is especially striking in these abnormal forms.

Normoblasts and erythroblasts appear in the blood stream in myelophthisic anemia (carcinomatosis, leukemia), and in hemolytic anemias such as acute hemolytic anemia, sickle-cell disease, Cooley's anemia, and erythroblastosis. When they are present in large numbers, many atypical cells are seen

(*i*) STIPPLING, GRANULES, NUCLEAR REMNANTS, AND INCLUSION BODIES IN RED CELLS

Stippled red cells (punctate basophilia) Stippling denotes the presence of round blue-purple granules of variable size scattered throughout the mature, polychromatophilic (*8*), or nucleated (*4a*) red blood cell Stippled red cells may be seen in films prepared with Wright's stain alone They are also evident in cresyl blue preparations, but should not be confused with the blue network of the reticulocytes.

Although stippling is a regular characteristic of lead poisoning, it may be seen in normal blood [66], in leukemia, and in practically all the anemias, especially in myelophthisic anemia and in Cooley's anemia and Cooley's trait

Siderocytes. Nucleated and nonnucleated forms of the red cell with siderotic granules which contain free iron have been termed siderocytes [79] Siderocytes are not shown in the plates but are described, since it is important to recognize and distinguish them from the punctate basophilia of stippled cells and from Howell-Jolly bodies When stained with Wright's stain, siderotic granules may appear singly as small blue-purple bodies or occur in pairs, or tetrads, near the periphery of the cell In contrast to the iron contained in hemoglobin, which does not stain, the free iron of the siderotic granule stains greenish blue with the Prussian blue reaction

chamois

or with acid-iron stain (*Syllabus*, Unit 7, p 72). Siderocytes have been seen in the embryo and in nucleated red cells of the bone marrow of the adult, but not in the mature erythrocyte of the normal adult [54] Large numbers may be seen in hemolytic anemia, especially after splenectomy [138].

Howell-Jolly bodies (nuclear remnant, *11*) Howell-Jolly bodies are small (1 to 3 μ), purple-blue, round bodies which may occur singly or in multiples in the red cell They are stained the same as the nuclei of normoblasts and are considered to be remnants of the nucleus [128] The cells containing Howell-Jolly bodies (*11*) should be compared with the normoblasts just above In the normoblast, the nucleus apparently is being extruded while two fragments of the nucleus — the size of Howell-Jolly bodies — remain The diameters of these bodies may vary from that of a small nucleus down to 0 5 μ Howell-Jolly bodies are seen in severe anemias such as pernicious anemia, Cooley's anemia, erythroblastosis, and certain myelophthisic anemias. They are increased in the blood of normal persons following splenectomy [110], and appear to be found characteristically in patients with atrophy of the spleen [18] in a variety of conditions including sprue and nontropical sprue

Cabot ring forms (*10*). Red cells in certain anemias occasionally show a delicate violet threadlike structure in the form of a ring or twisted ring or figure eight. Cabot [23] originally described these structures and considered them to be remnants of the nuclear membrane Schleicher [159], however, has presented evidence that the rings are artifacts due to formation of denatured protein The rare occurrence of these rings has made study of them difficult

Refractive granule of red blood cell (*9*) A refractive body about 0 5 μ in diameter occurring in less than 1 percent of normal red cells was described by Isaacs [96] This granule, which occurs singly, appears black in one focal plane of the microscope and clear and colorless (refractive) in another It does not take any ordinary stains and is of unknown origin and composition The occurrence of granules is similar to that of the reticulocytes, but red cells containing granules are considered to represent a more mature or intermediate, stage between the reticulocyte and the mature erythrocyte

Heinz-Ehrlich bodies Refractive bodies in red cells, described by Heinz [89] and by Ehrlich [59], are seen only in wet preparations and are not stained by Romanowsky stains They appear in the red cells as round refractile inclusion bodies with Brownian movement, varying in diameter from 0 5 to 1 μ They appear to be newly formed particles containing protein (of unknown origin) and occur in the course of irreversible injury to the red cell by certain toxic agents [69, 181] In contrast to the refractive granule of Isaacs, the Heinz-Ehrlich bodies are associated with hemolytic anemias from such compounds as phenylhydrazine, erythrol tetranitrate, sulfonamides, and certain oxidant compounds (*Syllabus*, Unit 7, p 72).

(*j*) Abnormal Shapes of Red Cells. The terms *anisocytosis* (abnormal variation in size) and *poikilocytosis* (abnormal variation in shape) have been used too loosely in describing the red cells in pathologic conditions Instead of using these terms, it is of greater diagnostic value to observe and describe the particular abnormal forms and associate them with a specific disease entity For example, the presence of polychromatophilic macrocytes usually means active regeneration of blood, which may be due to hemolytic anemia, acute blood loss, or response to therapy The presence of definite sickled forms (*17b*) is diagnostic of the sickle-cell phenomenon, but the phenomenon should be confirmed by a specific test.

Spheroidal red cells (spherocytes, *12*) The spheroidal red cell is a small deeply stained cell without central pallor, in which the hemoglobin appears increased Since the volume of the spherocyte is approximately normal but its diameter is less than normal, it is apparent, geometrically, that its thickness is increased Microscopically, the thick layer of hemoglobin appears dense and this appearance has led to the use of the term "hyperchromia" However, the hemoglobin content is normal, and these red cells, as well as others, never contain more than the normal concentration of hemoglobin — are never supersaturated Spheroidal red cells have increased osmotic and mechanical fragility, and they occur in congenital hemolytic jaundice (hereditary spherocytosis), in other hemolytic anemias such as acquired hemolytic anemia, following thermal burns [160], and in certain drug intoxications [62] (*Syllabus*, Unit 14, pp 179 and 180)

Oval cells (elliptic cells). Oval macrocytes (*14a*) are a characteristic cell type which is usually seen in the blood film of untreated pernicious anemia However, oval cells (*14b*) that are approximately normal in size are occasionally seen in increased numbers as an inherited Mendelian dominant characteristic without anemia [167] A comprehensive study of 86 cases in three interrelated families was made by Wyandt, Bancroft, and Winship [192] Although a few individual patients with oval cells have had other blood dyscrasias by coincidence — such as pernicious anemia, leukemia, or hemolytic jaundice — the presence of oval cells does not indicate a pathologic condition Although some cases reported in the literature have been confused with sickle-cell anemia, oval cells do not sickle

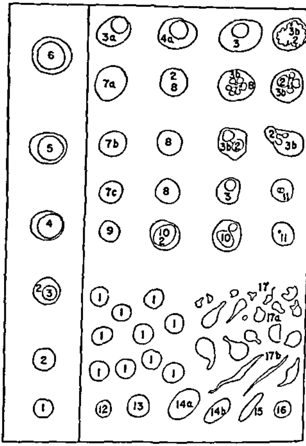
Pencil forms (*15*) The pencil form of red cells, which

PLATE I TYPICAL CELLS OF THE RED-CELL SERIES

Key:

1 Normal red cell
2. Polychromatophilic cell
3 Normoblast
3*a* Normoblast with reticulum * (reticulocyte)
3*b*. Normoblast with dividing nucleus
4. Late erythroblast
4*a* Late erythroblast with polychromatophilia and stippling
5 Early erythroblast
6 Proerythroblast
7*a* Early reticulocyte *
7*b*. Intermediate reticulocyte *
7*c* Late reticulocyte *
8. Stippled cell
9 Refractive granule of red cell
10 Cabot ring forms
11 Howell-Jolly bodies
12. Spheroidal red cell
13. Round macrocyte
14*a* Oval macrocyte
14*b*. Oval normocyte
15 Pencil form
16 Target form
17. Irregular forms
17*a* Pear-shaped or tailed forms
17*b* Sickled forms

* Vitally stained with brilliant cresyl blue before being counterstained with Wright's stain

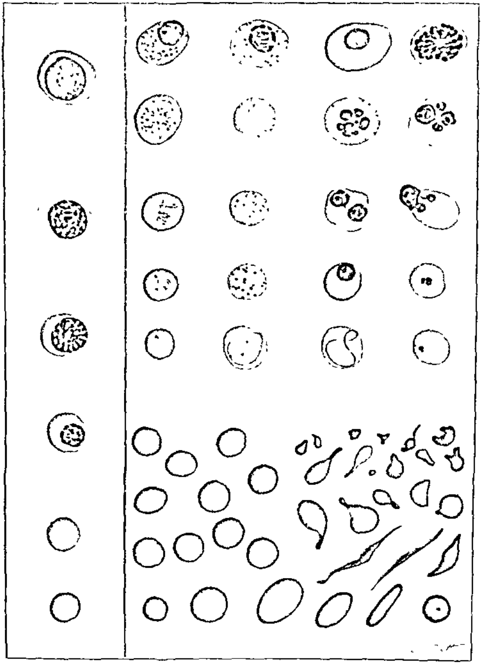


may be confused with the oval cells, is thinner in proportion to its length than the oval cell Pencil forms are usually hypochromic and are characteristically found in hypochromic anemia, Cooley's anemia, and Cooley's trait

Sickled cells (17b) Sickled forms of red cells are sometimes, but not always, seen in the film of peripheral blood of a patient with sickle-cell anemia These may take the forms shown in Plate I (*17b*) or they may have more rounded ends Those with rounded ends are permanently (irreversibly) sickled forms [161] Those with pointed ends or filaments, seen in freshly sickled preparations, may not be evident in the untreated film of peripheral blood (see Plate VI)

Target cells (16) The "target" cell has created more interest and been described by more names (Mexican hat, button form, bull's-eye) than it deserves Because of its unique arrangement of hemoglobin, it looks like a target, that is, there is a central area of hemoglobin (bull's-eye), surrounded by a clear ring without pigment outside of which is the pigmented border of the cell These cells are thin hypochromic cells which show an increased resistance to hemolysis in hypotonic solutions of sodium chloride [7, 81] They are seen in *increased numbers in severe hypochromic anemia, sickle-*cell anemia, Cooley's anemia and trait, and in liver disease, and are often increased in number following splenectomy [163] Target cells may be produced in vitro by suspending normal red cells in plasma or serum, rendered hypertonic either by addition of chemicals or by evaporation [176]. It is possible to see target cells in certain areas of a film of normal blood, their presence, however, may be due to abnormal drying of the film and should not be considered typical of the blood picture unless it is seen throughout the film

Irregular forms (poikilocytes, *17, 17a*) A variety of terms — such as pear-shaped, tailed, or bizarre forms — are used to describe the irregular forms of cells seen in certain of the red-cell diseases. It is unknown by what mechanism these forms arise, whether fragmentation of red cells, budding of the cytoplasm to produce daughter cells, or defective formation of cells [*33, 52,* 154] Small round particles containing hemoglobin were called schistocytes by Ehrlich [61] It is known that fission of the red cells occurs as a result of heating [84, 97] Tiny microcytes are often seen in the blood in hypochromic anemia, pernicious anemia, and Cooley's anemia The presence of a variety of these shapes and of



microcytes is a characteristic feature and aids in the diagnosis of Cooley's anemia

Lunar forms. Lunar or half-moon forms have been seen in acute hemolytic anemia (Plate VII). "Shadows" or ghosts of erythrocytes, thin veils of membrane, and "crescent bodies" — colorless veillike disks 40 to 50 μ in diameter with pink crescents in the margin — are found only rarely as a result of hemolysis [186].

3. *COUNTING RETICULOCYTES.* In a dry or a wet preparation, the number of reticulocytes is determined by counting a total of 1000 red cells. All red cells, including nucleated forms, that contain reticulum are counted as reticulocytes. The results are usually expressed as a percentage of the total number of red cells; or the absolute number of reticulocytes per unit volume may be calculated from the red-cell count. Because of the large number of cells in an oil-immersion field, it is helpful to cut down the area by inserting, in one ocular of the microscope, a mask that has a central hole 3 to 5 mm in diameter Different areas where the film is thin and the cells are separated, well stained, and easily identified should be selected for counting

Counterstaining the vitally stained preparation with Wright's stain, although not essential, gives a sharp contrast between the blue of the reticulum and the red of the cell No polychromatophilic cells should be present if the film is sufficiently stained with brilliant cresyl blue A film that is poorly stained should be discarded Precipitated stain is often confused with reticulum, but may be recognized because it occurs outside as well as on the red cells, it may be avoided by thorough washing after staining and frequent filtering of the cresyl blue and Wright's stain Platelets superimposed on red cells may also be confused with reticulum. Reticulum is definitely blue, whereas the granules of platelets are purple. The amount of reticulum varies from a dense network of disconnected but multiple blue particles to one or two small particles Any cell containing material recognizable as reticulum is included in the reticulocyte count (*Syllabus*, Unit 7, p 67)

The normal values for reticulocytes vary slightly with the method employed but are usually in the range of 0.5 to 1 5 percent The number of reticulocytes should be as great as, or greater than, the number of polychromatophilic cells seen in a smear taken simultaneously but stained only with Wright's stain.

4 *DETERMINATION OF VARIATION FROM THE NORMAL IN SIZE, SHAPE, AND HEMOGLOBIN CONTENT OF RED CELLS* A careful study of the blood film will show the variation from normal of the morphologic characteristics of the red cells in respect to size shape, and hemoglobin content When these abnormalities are striking there is little difficulty in classifying the cells as macrocytic, normocytic, or microcytic, and as normochromic or hypochromic. When the changes are slight, it is necessary to compare the cells with those of a normal individual

(*a*) COMPARISON WITH A FILM OF NORMAL BLOOD It is always possible to have at hand a normal film that may be interchanged with the abnormal film and observed under the microscope for comparison with an *unknown film* For a direct comparison with a normal film a satisfactory preparation of the unknown blood stained with Wright's stain is mounted on a glass slide with the blood film up A film of normal blood on a coverglass, also stained with Wright's stain, is then mounted with immersion oil, stained side down, on top of the unknown film. The two films are then face to face and can be focused upon alternately and quickly, using the oil-immersion objective, so that the unknown and normal red cells can be compared for size, shape, and hemoglobin content The films are of necessity placed in this manner, because in any other combination they are separated by too great a distance to permit focusing with the oil-immersion lens on the lower film (*Syllabus*, Unit 7, p 59).

(*b*) DETERMINATION OF MEAN CELL VOLUME AND HEMOGLOBIN BY THE WINTROBE METHOD [185] Any blood that shows significant variation from the normal should have a red-cell count, hemoglobin, and hematocrit with determination of the red-cell indices of Wintrobe (MCV, MCHC, MCH). These indices give the mean values for volume and hemoglobin concentration, but do not give any estimate of the degree of variation, which is evaluated by visual examination of the film or by the Price-Jones method described in the next paragraph These values should be compared and correlated with those observed in the films for size and hemoglobin concentration

(*c*) MEAN DIAMETER AND VARIATION OF DIAMETER AND THICKNESS OF RED CELL The mean size and variation in size of red cells can be determined by measurement of the cell diameters by the method of Price-Jones [144] The data can be shown graphically as a distribution curve, as shown in Fig 3, or can be analyzed statistically by arranging the frequency of occurrence of each group of diameters (using differences of $\frac{1}{4}$ μ) The mean cell diameter (MCD), the standard deviation of the diameter from the mean, and the coefficient of variation are determined. The standard deviation of the diameters of a population of red cells expresses quantitatively the degree of variation from the mean diameter Since the absolute values for the mean diameter vary in different conditions, the more useful statistical measure for comparison of results is the coefficient of variation from the mean diameter, which is expressed in percent (Table 1)

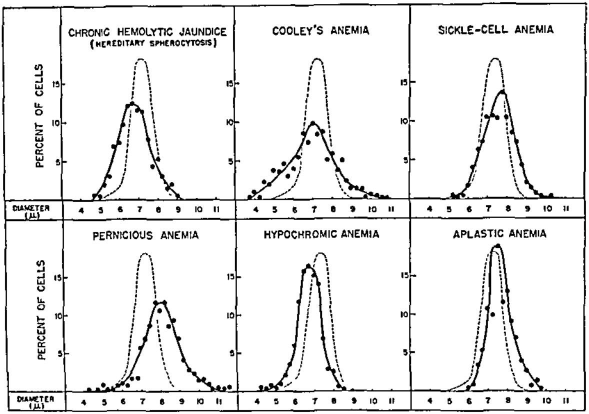


FIG 3 Typical curves of the frequency distribution of red-cell diameters in six examples of anemia compared in each instance to a curve (dotted line) derived from ten normal subjects (see Table 1)

TABLE 1 DATA FOR THE FREQUENCY-DISTRIBUTION CURVES OF RED-CELL DIAMETERS SHOWN IN FIG 3 *

Diagnosis	Red-cell count (10^6/mm^3)	Hemoglobin (gm/100 ml)	Hematocrit (percent)	Mean corpuscular volume, MCV (μ^3)	Mean corpuscular hemoglobin concentration, MCHC (percent)	Mean cell diameter, MCD (μ)	Standard deviation of diameter, σ (μ)	Coefficient of variation of diameter (percent)	Mean cell thickness, MCT (μ)
	Mean values for 10 normal individuals								
Normal subjects	4.81	14.7	44.7	93	33	7.2	0.50	7.0	2.3
	Chronic hemolytic anemias, characterized by hereditary defects of the red cells								
Congenital (chronic) hemolytic jaundice	3.34	10.0	29.7	89	34	6.83	0.80	11.8	2.43
Cooley's anemia	3.82	7.2	27.7	73	26	6.92	1.27	19.8	1.93
Sickle-cell anemia	3.46	7.8	24.8	72	31	7.61	0.84	10.5	1.65
	Anemias due to decreased production of red cells								
Pernicious anemia	1.16	4.2	14.5	125	29	8.10	1.01	12.5	2.43
Hypochromic anemia	2.72	4.2	16.7	61	25	6.70	64	9.5	1.74
Aplastic anemia	1.48	6.0	16.1	109	37	7.7	71	9.2	2.34

* The indices (mean corpuscular volume, mean corpuscular hemoglobin concentration and mean corpuscular hemoglobin) were calculated according to Wintrobe [185] The mean cell diameter was measured according to the method of Price Jones [144], standard deviation and coefficient of variation also being determined The mean thickness of the cells was calculated from this mean volume and mean diameter according to the method of von Boros [17] on the assumption that the red cell is a right circular cylinder of known volume and diameter

As shown in Fig. 3, three hereditary anemias are characterized by abnormalities of the geometry of the red cells In congenital hemolytic jaundice, the mean cell diameter is decreased, so that the red cells appear microcytic on the blood film However, the mean cell volume (MCV) is normal or slightly macrocytic, so that the mean cell thickness (MCT) is abnormally increased and the cells are more spheroidal than normal, a fact that renders them more susceptible to osmotic and mechanical hemolysis [17, 28, 81] In sickle-cell anemia, the mean diameter is increased, so that the red cells appear macrocytic on the blood film However, the mean cell volume is not macrocytic, but normal or slightly decreased, so the thickness is decreased The increased flatness of these cells renders them less susceptible to osmotic hemolysis. In Cooley's anemia, which is usually microcytic, the coefficient of variation of the diameters is greater than in any other anemia and the number of microcytes predominates over the macrocytes

In pernicious anemia, the coefficient of variation is also large, greater than in any other macrocytic anemia [39] In many instances of aplastic anemia, the cells may be macrocytic, but the distribution of the diameters is approximately normal. In hypochromic anemia, the variation in diameter of the red cells is not so marked as in Cooley's anemia, although the cells show an increasing degree of microcytosis and variation in diameter as the iron deficiency increases.

6. THE WHITE CELLS

1 *INTRODUCTION* The white blood cells are divided into five separate series, namely, granulocytic, lymphocytic, plasmacytic, monocytic, and histiocytic [34] The maturation and nuclear structure of the cells in each of the first four of these series are illustrated diagrammatically in Figs 4, 5, 6, and 7 The structure of histiocytic cells is shown in Fig. 8. It is not always essential, when a differential count is made, to subdivide each series into as many stages as are shown in the figures, but it is necessary to recognize these stages in order to understand the degree of maturity of each cell. In general, the more immature the cells, the more serious is the prognosis in diseases of the blood and in physiologic responses Typical cells representing each stage are described It is not always possible to classify the cells since there are many intermediate stages, and abortive and abnormal forms Sometimes the nucleus develops faster than the cytoplasm and sometimes the cytoplasm is more mature than would be expected with the structure of the nucleus Typical cells seen in normal blood are shown in Plate II

2 *GRANULOCYTIC SERIES* (Fig 4 and Plates II and X)

(*a*) Neutrophil (polymorphonuclear neutrophil, granulocyte, Plate II, *3, 3a*) The neutrophil has a diameter of approximately 10 to 15 μ The nucleus shows two or more distinct lobes connected by bands or threads of chromatin, and is made up of coarse condensed masses of purple-staining chromatin The cytoplasm is pink to lilac The granules, if present, are fine and have the color of the nucleus (neutrophilic)

Abnormal forms Hypersegmented or multilobed neutrophils are found in untreated pernicious anemia, although they may occur in other conditions Round or oval basophilic areas in the cytoplasm, known as Dohle bodies, may be seen in certain infections In certain other infections, toxic granules which appear as blue-black, coarse granules may occur in the cytoplasm Occasionally these granules are mistaken for those of the basophil

(*b*) Eosinophil The eosinophils are a little larger than neutrophils This is especially true when the cells are poured forth in large numbers, as in certain infestations, such as trichiniasis, or other pathologic states The nucleus is usually bilobed or a band form (Plate II, *5a, 5b*) The cytoplasm is usually lilac to blue, but may be difficult to see because of the large number of granules. The granules are much larger than those seen in the neutrophil or in any other cell They are a bright orange-red in color and sharply defined or round in outline They often appear over the nucleus, as well as free in the cytoplasm.

(*c*) Basophil Basophils are usually a little smaller than the mature neutrophil. The nucleus is lobulated as in the neutrophil. The cytoplasm is usually lilac to blue. Large distinct blue granules are generally scattered throughout the cell and may be so numerous as to obscure the structure of the nucleus

(*d*) Young Granulocyte or Band Form (stab, young form, Plate II, *4*) The band forms of the neutrophil are immature cells which are often slightly larger than the mature forms with the corresponding granulation There may also be band forms of the eosinophil and basophil The nucleus of the cell is not segmented. The cytoplasm is that of the corresponding adult cell The granules are the same as those of the adult cell of the series having fine purple granules in the young neutrophil, large blue granules in the young basophil (Plate II, *6a*), and red-orange granules in the eosinophilic cell The band form is the predominating cell in Pelger's anomaly [95]

(*e*) Metamyelocyte The nucleus is round, indented, or kidney-shaped, and the clumps of chromatin

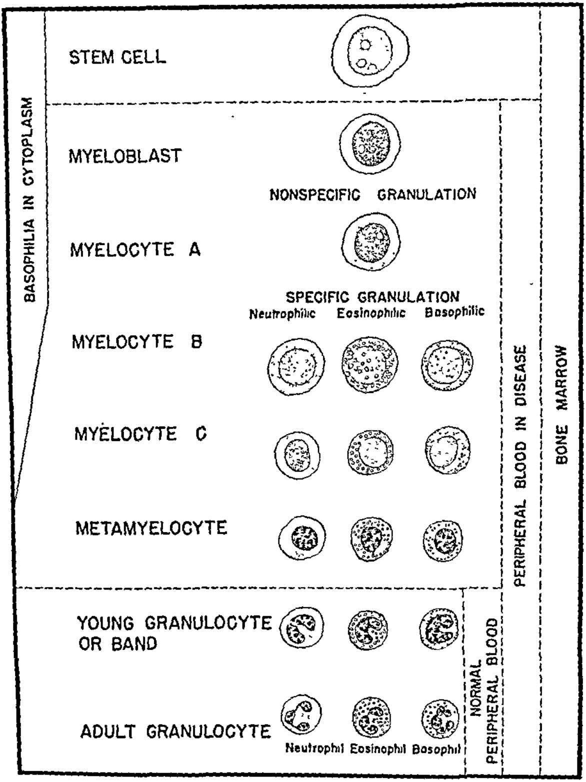


Fig 4 Diagram of the maturation of the granulocytic series

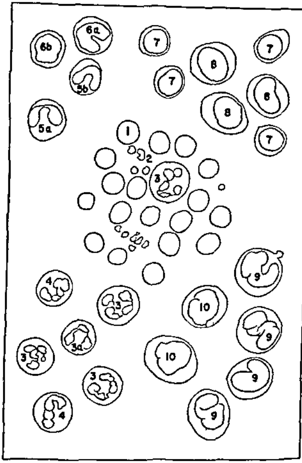


PLATE II. TYPICAL CELLS OF NORMAL HUMAN BLOOD

Key:

1 Normal red cells
2. Platelets
3 Neutrophil, adult
3*a*. Neutrophil, adult *(two lobes)*
4. Neutrophil, band form
5*a* Eosinophil, two lobes
5*b* Eosinophil, band form
6*a* Basophil, band form
6*b* Metamyelocyte, basophilic
7. Lymphocyte, small
8 Lymphocyte, large
9. Monocyte, mature
10 *Monocyte, young*

are not so deeply stained as in the older cells The cytoplasm and granules are similar to those of the corresponding adult cell

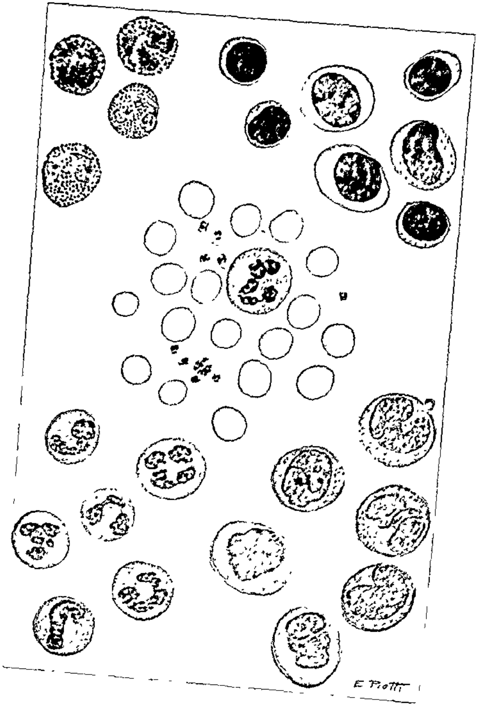
(*f*) MYELOCYTE C (late myelocyte) The nucleus is round and quite distinct in outline The smooth structure *of the nucleus is contrasted with the clumped chromatin* of the more mature forms The cytoplasm is more basophilic than in the metamyelocytes or later forms Granules may be neutrophilic, eosinophilic, or basophilic, and, if present, are in the cytoplasm and are *not* seen over the nucleus

(*g*) MYELOCYTE B This cell is usually much larger than the more mature cells of this series (12 to 18 μ) The nucleus, which may be round or oval, is less sharply defined than in any other cell The chromatin structure is rather homogeneous The cytoplasm of the cell is more basophilic than in the older cells The granules are scattered throughout the entire cytoplasm and *cover* the nucleus Often the contour of the nucleus is obscured by the granules The granules may be neutrophilic, eosinophilic, or basophilic (or specific) The eosinophilic and basophilic granules are larger than the neutrophilic granules, but smaller than the corresponding type of granule in the older cells (This is the earliest stage in which specific granulation appears)

(*h*) MYELOCYTE A (promyelocyte) The nucleus is a deep red-purple, with a fine granular structure *Nucleoli may or may not be present A nucleolus is a* small, round, sharply defined area in the nucleus that takes a light-blue stain The cytoplasm is a deep blue. A few scattered red-purple or azurophilic granules appear These granules are usually nonspecific, since differentiation into neutrophilic, eosinophilic, and basophilic granules takes place at a more mature stage (myelocyte B)

(*i*) MYELOBLAST The nucleus is red-purple with a finely granular or homogeneous chromatin structure There are usually one to three nucleoli present in the form of round blue areas The intensity of color of the nucleus is often less than that of the cytoplasm The cytoplasm is intensely basophilic No granules are present It may be impossible to distinguish the myeloblast from other blast forms

(*j*) STEM CELL (same as described above, p 8).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3 *LYMPHOCYTIC SERIES* (Fig. 5 and Plates XII and XIV).

(*a*) SMALL LYMPHOCYTE (Plate II, *7*). The small, adult lymphocyte is the smallest white cell (7 to 10 μ) The nucleus is deep purple and usually about the size of the red cell The round nucleus is made up of masses of chromatin, so that no distinctive internal structure is seen The periphery of the nucleus is usually defined rather sharply. The cytoplasm forms a narrow rim around the nucleus This cytoplasm should be a clear light blue, but often in thick or heavily stained smears the color is rather dark Occasionally red-purple granules and, more rarely, blue granules are present in the cytoplasm These granules, however, are few, distinct, and scattered, and should not be confused with the finer granules of the monocyte

(*b*) LARGE LYMPHOCYTE (Plate II, *8*). The large lymphocyte varies in diameter from 10 to 18 μ and may be as large as a monocyte. The nucleus is usually somewhat larger than in the small lymphocyte and is often irregular in shape, and the chromatin masses are not clumped quite as much as in the small lymphocytes and may sometimes have a smooth appearance. The cytoplasm is a clear light blue and is much greater in proportion to the nucleus than in the small lymphocyte. Occasionally red-purple *granules* may be scattered through the cytoplasm.

(*c*) YOUNG LYMPHOCYTE The young lymphocyte occurs occasionally in normal bloods, and frequently in children's blood and in the blood in infectious states. This cell is the size of the large lymphocyte, but the nucleus fills a greater proportion of the cell Chromatin masses of the nucleus are not so condensed as in the older forms, but do not resemble the fine structure of a blast form A deep-blue basophilic cytoplasm is characteristic of these young cells. No granules are present

(*d*) LYMPHOBLAST The red-purple nucleus is made up of finely granular chromatin, with or without nucleoli, as in other blasts. The cytoplasm of the cell is deeply basophilic, as *is characteristic of other blast forms* Sometimes there is a clear perinuclear area in the cytoplasm Occasionally blasts appear with almost no cytoplasm but containing the characteristic nucleus Granules are absent The lymphoblast may be indistinguishable from other blast forms

(*e*) STEM CELL (same as described above, p 8)

(*f*) ATYPICAL LYMPHOCYTES (Plate XIV) Among the abnormal cells of the lymphocytic series, those seen in infectious mononucleosis are of especial interest. These cells vary markedly in their characteristics but three definite types may be recognized These abnormal forms may be seen in normal blood in small numbers, but are seen in increased numbers in infectious mononucleosis, infectious hepatitis, chicken pox, and serum sickness.

One variety of atypical lymphocyte may be seen that is larger than the large lymphocyte and usually of irregular shape (appearing to have many sides). The irregular periphery gives the appearance of a distorted cell, and the presence of so many of these irregularities of outline suggests that these cells are abnormally fragile. The *cytoplasm is a hyaline blue without granules* The intensity of blue may be increased along the margin of the cell as if the cytoplasm were thicker or condensed along the edge. The irregular nucleus is often more reticular and more wavy than that of the normal lymphocyte, and for this reason may be confused with the monocyte.

A second variety of atypical lymphocyte includes cells of large size and irregular shape similar to the first variety. *The chief characteristic of the second variety* is the deep muddy-blue color of the cytoplasm Although this basophilic cytoplasm is typical of immature cells or blast forms, the nuclear structure is quite mature in appearance, the nuclear chromatin occurring in wavy masses. Granules are usually absent.

In a third variety of atypical lymphocyte, the cytoplasm is vacuolated in variable degree If the vacuolation is marked, it may give a "foamy" appearance The cytoplasm may be light blue or a very deep blue

4 *PLASMACYTIC SERIES* (Fig 6 and Plate XIII)

(*a*) PLASMA CELL (plasmacyte). The nucleus of the plasma cell (plasmacyte) has a very characteristic *coarse, deeply stained, clumped chromatin structure.* This nucleus is usually eccentrically placed in an oval or elongated cell. The cytoplasm is a gray-green-blue with a spongy appearance There are often vacuoles in the cytoplasm Globules or clear areas in the cytoplasm *taking an acid stain are called Russell bodies* These may occur singly or in groups, or they may rupture to make a larger, irregular, acidophilic area often seen around the edge of plasma cells The edge of the cytoplasm may be very ragged or fringed. Granules are rare in the plasma cell, but basophilic granules may occur. Large basophilic granules which appear following treatment with stilbamidine resemble inclusion bodies.

(*b*) YOUNG PLASMA CELL The young plasma cell is *usually larger than the adult plasma cell and has been* described as the "multiple myeloma" cell The nucleus has a finer structure than that of the adult cell, the chromatin often occurring in smaller clumps, sometimes granular The nucleus is not necessarily eccentric in position The color of the cytoplasm is the same gray-green-blue as the adult cell, but may be more intense The spongy appearance may be evident and vacuoles may be present

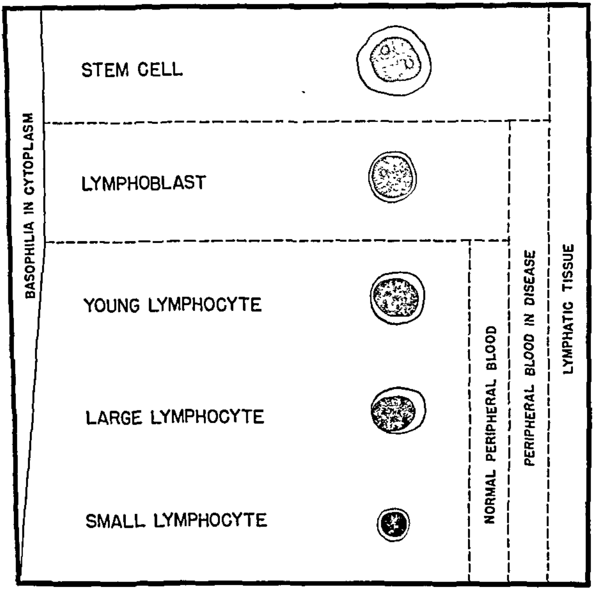

FIG 5 Diagram of the maturation of the lymphocytic series

(*c*) PLASMABLAST The nucleus has a fine granular structure that is typical of all blasts One or more large, sharply defined nucleoli are present The cytoplasm has the gray-green-blue color that is characteristic of this series of cells Vacuoles may be present The plasmablast may not be distinguishable from other blast forms in some instances

(*d*) STEM CELL (same as described above, p 8)

(*e*) ABNORMAL FORMS The presence of large, irregular plasma cells with characteristic nuclei, but with abundant cytoplasm and indefinite ragged peripheries, sometimes with streamers of cytoplasm, may be of significance and not artifactitious Although the eccentric nucleus is characteristic, it should be recognized that in pathologic conditions there are abortive forms and this

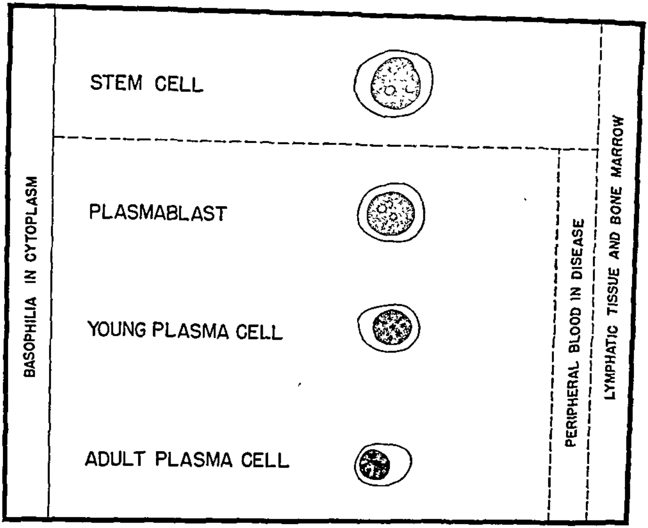

FIG 6 Diagram of the maturation of the plasmacytic series

ditions, such as plasmocytoma, there are often abnormally large forms, *and sometimes cells with more than* one nucleus

(*f*) COMPARISON OF PLASMA CELLS WITH OTHER CELLS The color of the cytoplasm in the plasmacytic series is a characteristic gray-green-blue, the younger forms being a deeper more intense blue This blue is *much deeper than that seen in the cytoplasm of any* lymphocyte and a deeper gray-blue than that seen in other blast forms The cytoplasm of the plasmacytic series is sometimes confused with that of the monocyte, but lacks the granules of the monocyte and is a much deeper blue and more opaque in appearance

5 *MONOCYTIC SERIES* (Fig 7 and Plate XI)

(*a*) MONOCYTE (Plate II, *9*) The monocyte is larger than most of the other cells that are found in the normal peripheral blood (13 to 20 μ) The nucleus is indented or lobulated, often presenting a folded appearance *The structure of the nucleus is looser than that of* any of the other cells, as if it were made up of a network of chromatin Because of this lacy structure, the nucleus appears to be stained lighter purple than the nuclei of other cells The cytoplasm is a gray-blue, in contrast to the clear light blue of the lymphocytes The *granulation varies in different cases* The monocyte usually contains fine neutrophilic granules, although in some cells the red-purple granules are scattered throughout the cytoplasm The amount of granulation varies from none to a dense stippling of fine granules

(*b*) YOUNG MONOCYTE (Plate II, *10*) The nucleus in the young monocyte is round, but the same lacy folded type of nucleus is seen as is present in the adult monocyte The cytoplasm is the same gray-blue as in the adult form This cell should be compared with the

adult cell in a given smear to differentiate the cell from the lymphocyte or the metamyelocyte. The granules are the same as in the adult cell

(*c*) MONOBLAST The nucleus of the monoblast is much finer than in the older cells of the series, although the contour may be irregular, and it may have a certain folded appearance characteristic of the adult cell. Although the chromatin is finely granular, it is more lacy than in the other types of blasts Nucleoli are usually present The cytoplasm is a deep blue, showing more gray-blue than in the myeloblast or lymphoblast. There may be red-purple granules in this blast form, even in the presence of nucleoli Auer bodies, which appear as short red rods or splinters, are frequently present in the monoblast.

(*d*) STEM CELL (same as described above, p 8).

6 *HISTIOCYTIC SERIES* (Fig 8) The histiocyte, as seen in the peripheral blood and bone marrow, represents a series of cells that are derived from the reticulo-endothelial tissue throughout the body and can be differentiated from other series of white cells, such as the monocytic.

Histiocytes have been referred to by many terms, such as large mononuclear leukocytes, macrophages of Metchnikoff, 1892; endothelial leukocyte of Mallory, 1898, adventitial cells of Marchand, 1898; clasmatocyte of Ranvier, 1900, and of Sabin, Doan, and Cunningham, 1923-24; histiocyte of Aschoff and Kiyono, 1913, endothelial phagocyte of Foot, 1925, and monocyte by many investigators in recent years [70, 157, 158] Much experimental and clinical work on histiocytes is difficult to interpret because the cells were classified as monocytes

Histiocytes may be present in the peripheral-blood film of normal individuals, up to 3 or 4 percent according to Sabin and Doan [157], who examined fixed preparations stained with Wright's stain as well as by the use of the supravital technique

The appearance of histiocytes varies greatly in the same blood film, in different samples from the same individual, and in samples from different individuals under pathologic conditions This variation in the type of cell seen may be related to the tissue from which the cells arise (spleen or lymph nodes) and to the process for which they are elaborated In histiocytic leukemia, the histiocytes, which may be markedly increased, are probably the result of abnormal growth of a particular cell type with proliferation in the peripheral blood as well as tissues No maturation cycle has been established for the histiocytic series Nucleoli may be present in cells that do not show basophilic cytoplasm, while some of the most basophilic cells may lack nucleoli

Histiocytes are larger than the cells of the erythrocytic or white-cell series and usually are markedly *irregular in shape A few recognized types of histiocytes* are described since no single description is adequate

(*a*) HISTIOCYTE — AMOEBOID FORM The amoeboid form of histiocyte is larger than the monocyte or lymphocyte, but is often confused with them (Plate XI, *5*). The nucleus has a definite but delicate membrane, and is lighter in color than that of the lymphocyte or monocyte The nucleus may appear as a loose network or as a structure resembling a honeycomb There may be one or more small blue nucleoli. The abundant cytoplasm is a pale gray-blue so delicate that the cell membrane is quite difficult to discern The irregular shape of the cell resembles an amoeba, pseudopods of cytoplasm being very characteristic In some cells there appears to be endoplasm containing fine granules, surrounded by a clear, pale-blue ectoplasm The granules, if present, are fine and red-purple in color Irregular black particles or cellular debris may be present.

(*b*) HISTIOCYTE — PHAGOCYTIC FORM The phagocytic histiocyte is very large (15 to 80 μ) and irregular in shape The nucleus is light purple and reticular, sometimes with one or two nucleoli The cytoplasm is characterized by delicate lavender veils In the cytoplasm there may be vacuoles, as well as phagocytosed red cells, neutrophils, platelets, or cellular debris.

(*c*) HISTIOCYTE — BASOPHILIC OR BLAST FORM. The basophilic form of the histiocyte varies in size, but is larger than the other blasts. The nucleus is often irregular in shape with uniformly granular structure, the granulation being less marked than in the other types of blasts. Nucleoli may or may not be present The cytoplasm in some cells is deep blue and very irregular in contour, sometimes it is much lighter than would be expected in a cell with a blast type of nucleus Red-purple granules are often present even in these young forms

(*d*) HISTIOCYTES — LYMPHOCYTIC FORM (Fig 8 and Plate XIV) Large irregular cells with deep-blue cytoplasm often appear in association with an increase of lymphocytes and plasma cells and are usually classified as atypical lymphocytes It is difficult to identify the origin of these cells in some instances of virus infections, and it is quite probable that they are histiocytes from lymphatic tissue rather than lymphocytes

(*e*) HISTIOCYTES IN LIPOID-STORAGE DISEASES Large cells, irregular in shape and characterized by the spongy vacuolated cytoplasm, sometimes seen in the lipoid diseases, are histiocytes

(*f*) "HEMOHISTIOBLASTS OF FERRATA" Ferrata and Franco [67] described a large irregular cell, frequently seen in the blood of patients with chronic myelogenous leukemia, as a hemohistioblast The light-blue cytoplasm may be clear, spongy, or granular The type of

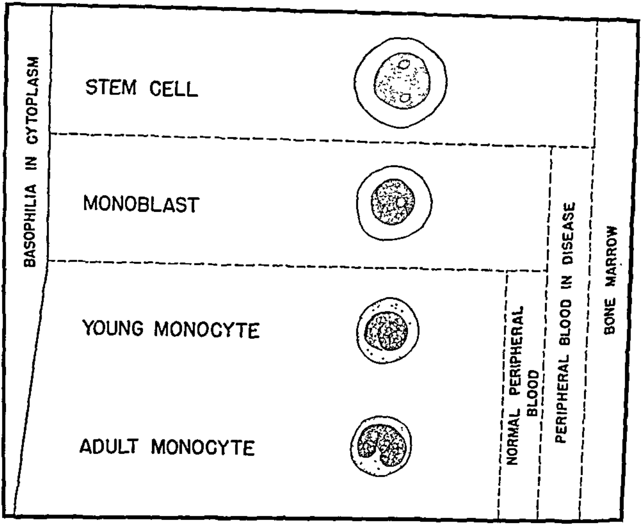

FIG 7 Diagram of the maturation of the monocytic series

FIG. 8 Diagram of histiocytes observed in peripheral blood in selected clinical cases

1 *Subacute bacterial endocarditis* These histiocytes show evidence of amoeboid activity and phagocytosis The cell in the center contains a red cell that has been phagocytosed A red cell is shown in the upper corner for comparative size

2 *Typhoid fever* Vacuoles are present in the nuclei

3. *Reticulum-cell sarcoma* The histiocytes show vacuolation and evidence of phagocytosis Nucleoli are present in the two lower cells A vacuole is present in the nucleus and seven vacuoles occur in the cytoplasm of one of the upper cells There is a vacuole in the cytoplasm of one of the other cells

4 *Severe anemia* The histiocytes in this blood film were very irregular in shape, with pseudopods It can be seen in the upper cell how easily a portion of the cytoplasm can be separated and appear free in the peripheral blood These cells also show vacuolization

5 *Hodgkin's sarcoma* The predominating white cells in this blood film were large cells with deep-blue cytoplasm, containing many vacuoles in both the nucleus and the cytoplasm

6 *Histiocytic leukemia* The histiocytes were varied in type in this blood, many showing evidence of amoeboid activity and phagocytosis

7 *Histiocytic leukemia* The histiocytes in this case showed evidence of marked amoeboid activity and phagocytosis of red cells (as seen in the cell at the left) and other foreign matter (as seen in the two upper cells)

8 *Histiocytic leukemia* In this blood film, the cells were much larger than a lymphocyte or lymphoblast The nuclear structure was quite homogeneous but nucleoli were not present The cytoplasm was deep blue Evidence of active phagocytosis was seen

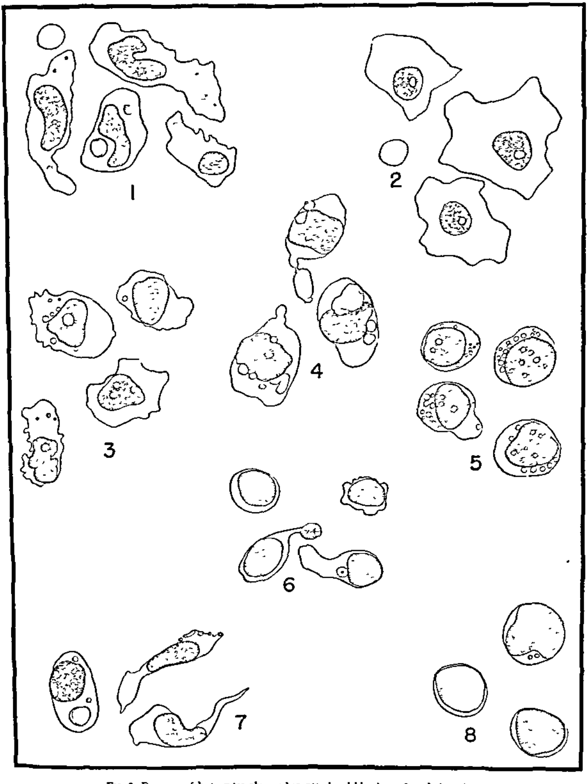

FIG 8 Diagram of histiocytes observed in peripheral blood in selected clinical cases

TABLE 2. WHITE-CELL COUNTS AND RELATIVE PROPORTION OF WHITE CELLS IN NORMAL ADULTS, AS REPORTED BY SEVERAL OBSERVERS

		Osgood and Ashworth [136]	Wintrobe [185]	Stetson [166]	Hamre and Au [85]	Snell, Neel, and Ishibashi [165]	Mainland, Coady, and Joseph [114]
Number of Observations		236 & 378		62 counts on 6 normals	136	24	24
Age		14–30	normal adults	20–30	16–25		19–21
Sex		M and F		M	M	M	
White-cell count ($10^3/mm^3$)							
	mean	7 4	7 0	6 3	7 06	8 08	
	range	4 5–11 5	5 0–10 0	4 0–9 5			
	standard deviation				± 1 56	± 2 36	
Differential white-cell count (*percent*)							
Neutrophils	mean	55 6		51.0	54 6	60 6	56 9
	range	33 0–78 0	57 0–67 0	40 0–63 0			
	standard deviation				± 8 0	± 7.7	± 5 9
Eosinophils	mean	1 9		2 3	2 9	2 8	2 0
	range	0–6 0	1–3 0	0–5 3			
	standard deviation				± 2 7	± 1 9	± 1 0
Basophils	mean	0 5		0 85	0 57		0 44
	range	0–2 0	0–0 7	0–3 5			
	standard deviation				± 0 48		± 0 20
Lymphocytes	mean	38 0		36 0	36 8	30 3	37 0
	range	*18–65*	*25–33*	*27–48*			
	standard deviation				± 6 9	± 6 5	± 5 9
Monocytes	mean	4 0		9 6	5 08	6 0	3 6
	range	0–9	3–7	4 5–15			
	standard deviation				± 1 47	± 2 6	± 0 8

granules may be eosinophilic, neutrophilic, basophilic, or azurophilic The nuclear structure is spongelike in character or like a honeycomb At least one nucleolus is usually present. These are also considered to be tissue cells or histiocytes [151].

7 *DIFFERENTIAL COUNT OF WHITE CELLS* The differential count of white cells is one of the basic examinations of the patient It is used for diagnosis and in following the course of the patient The white-cell count and differential white-cell count in normal individuals, as reported by different observers, are shown in Table 2 The quantitative limitations and significance of the results are discussed in the *Syllabus* (Unit 7, p 82) A careful enumeration is made of the white cells on the film, each type of white cell being classified In order that each cell may be counted only once, the slide is moved progressively and systematically from one field to the next covering as much of the film as possible to obtain representative distribution (*Syllabus*, Unit 7, p 61) The number of each class of white cells is determined and the results are expressed in percentage of the total number of white cells enumerated All abnormal white cells should be classified or described in detail and reported Some of the different types of abnormal white cells that may be seen in films of peripheral blood are described on pp 14 to 24 and in Table 3 Some other differential points in identifying the early cells are given in the next section Cells that are ruptured, fragmented, or degenerated ("basket" cells or "smudges") usually cannot be identified and are not included in the differential count, but may be noted separately and reported as the number seen per 100 white cells A significant number of broken cells may be seen in leukemic bloods The counts are performed in multiples of 100 cells, using one or two coverglass preparations At least 100 cells should be counted as a screening procedure.

When nucleated red cells are present in the blood film, they should be reported as the number seen while counting 100 white cells, but they are *not* included in the differential count of leukocytes If there are large numbers of nucleated red cells present, the stage in the erythrocytic maturation series should be noted, and an actual count made of the number of nucleated forms per 1000 red cells and the percentage determined From this figure the absolute number of nucleated red cells per cubic millimeter is calculated (*Syllabus*, Unit 7, p 62).

8 *DISTINGUISHING CHARACTERISTICS OF IMMATURE CELLS FREQUENTLY CONFUSED* The recognition of the blast form and its differentia-

tion from the more mature cells is of utmost diagnostic importance. Blasts have in common the characteristics of deeply basophilic cytoplasm, nuclei having finely and homogeneously granular chromatin structure, and frequent presence of nucleoli. In general, the presence of blasts in the peripheral blood is a sign of marked abnormality of the blood-forming organs and should lead to more extensive and repeated blood examinations. Nucleated red cells occurring in the peripheral blood at approximately a normal level of red cells may indicate extramedullary myelopoiesis or myelophthisis due to leukemia, lymphoma, or neoplastic invasion of the bone marrow.

The blasts of red cells should be readily distinguished from the blasts of white cells which often occur in the same blood film, since proerythroblasts or early erythroblasts with basophilic cytoplasm are usually present in association with the more mature nucleated red cells with polychromatophilic or hemoglobin-containing cytoplasm. In the proerythroblast the cytoplasm is more of a deep gray-blue than that seen in the white cells; the nucleus is usually definitely round and more red-purple than in the other blasts, nucleoli may or may not be present.

The recognition of the type of blast of the white-cell series is usually of academic interest. Identification may be difficult or impossible, and usually contributes little to the welfare of the patient. If blasts are present in association with more mature forms, this is presumptive, but not definite, evidence that the immature cells belong to this same series. Immature cells of the lymphocytic and plasmacytic series may be present in the same blood film in such a disease as infectious mononucleosis. In stem-cell leukemia or in some acute leukemias, because of the abortive cells present, differentiation is not possible. With a leukopenia the number of blast cells may be so small that the identification of the series to which they belong may be impossible. When a "buffy coat" or a concentration of these cells is made before preparing a film, the cells may be distorted so that the series to which the blast belongs cannot be determined. The myeloblast and lymphoblast are quite similar, although the lymphoblast often has less abundant cytoplasm. The plasmablast has the gray-green-blue basophilic cytoplasm that is characteristic of the mature forms of the series. The monoblast is usually larger than either the lymphoblast or the myeloblast, the nuclear structure is more reticular than in the other types of blasts, the nucleus is often folded or irregular in shape, granules are sometimes present in the deep-gray-blue cytoplasm. The size of the cells, the basophilia of the cytoplasm, the structure of the nucleus, and the presence of nucleoli should differentiate the blast forms from lymphocytes which, when mature, have a nucleus about the size of a red cell. For the distinguishing characteristics of other cells that are easily confused see Table 3.

TABLE 3 CHARACTERISTICS OF CELLS THAT ARE FREQUENTLY CONFUSED

Cells to be distinguished	Diameter (μ)	Cytoplasm		Nucleus				Granules	
		Color	Amount	Shape	Structure	Color	Nucleolus	Color	Number
Monocyte	13–20	Gray blue	Abundant	*Adult*, Indented *Young* Round	Reticular lacy, folded	Blue-purple	0	Purple and red purple	Few to many, 'peppered'
Lymphocyte									
small	7–10	Clear light blue	Scant	Round	Condensed chromatin	Deep purple	0	Red purple rarely blue	Few, scattered
large	10–20		Abundant	Round		Deep purple	0		
Neutrophil									
adult	10–15	Pink to lilac	Moderate	Segmented	Condensed chromatin	Purple	0	Fine purple	Few to many
young (band)	10–18		Moderate	Not segmented		Purple	0	Fine purple	Few to many
Metamyelocyte	12–20	Pink to lilac	Moderate	Round or indented	Slightly clumped	Purple	0	Fine purple	Few to many
Myelocyte C	15–20	Gray-blue	Moderate	Round	Homogeneous	Purple	0	Purple	Few to many
Histiocyte	15–50	Light gray-blue, spongy	Abundant or irregular	Irregular or round	Honeycomb, vacuolated	Purple	±	Varied, also phagocytic particles	Rare
Plasma cell	10–25	Gray green blue	Abundant	Round	Wedges of chromatin	Deep purple	0	0	Rare
Proerythroblast	15–25	Deep blue	Small	Round	Homogeneously granular	Red purple	+	0	0
Early erythroblast	10–20	Gray blue	Moderate	Round	Finely divided chromatin	Purple	0	0	0
Late erythroblast	10–20	Blue to lavender	Moderate	Round	Coarse clumping of chromatin	Purple	0	0	0
Normoblast	7–15	Pink to lavender	Variable	Round	Condensed chromatin	Deep purple	0	0	(stippling)

7. THE PLATELETS AND THE THROMBOCYTIC SERIES

1. *ORIGIN.* Although there have been many theories about the origin of platelets, that presented by Wright [190] has been the most generally accepted. Wright showed that small hyaline bodies containing red-purple granules were detached fragments or pseudopods of the megakaryocytes of the bone marrow that appeared as free formed elements in the peripheral blood The differential-staining property of Wright's modification [191] of the Romanowsky stain was an important factor in establishing the relation between the granule-containing cytoplasm of the megakaryocyte and the platelets Other evidence given in support of Wright's theory of platelet formation is (*a*) platelets are not seen in the embryo until after the appearance of the megakaryocytes; (*b*) blood platelets and megakaryocytes are found only in mammals; (*c*) the number of platelets in the blood roughly parallels the number of megakaryocytes in the bone marrow in certain diseases or physiologic conditions Wislocki, Bunting, and Dempsey [189] have shown with histochemical methods that there are points of similarity between blood platelets and the cytoplasm of megakaryocytes The evidence indicates that platelets are cytoplasmic rather than nuclear in origin and probably arise from megakaryocytes.

2 *DESCRIPTION OF NORMAL AND ABNORMAL FORMS OF THE THROMBOCYTIC SERIES* (Fig 9).

(*a*) Platelet or Thrombocyte The platelets are formed elements of the blood, measuring 2 to 5 μ in diameter, that appear as a clump of red-purple (azurophilic) granules in a light-blue cytoplasm that is almost transparent Although true nuclei do not occur in platelets, the granules may be aggregated in a sharply outlined mass in the central part of the platelet, resembling a nucleus When the blood film is vitally stained with brilliant cresyl blue before the Wright's stain, as for reticulocytes, the cytoplasm is intensely stained with the blue Sometimes the platelet is devoid of granules, appearing as an irregular mass of cytoplasm At other times the platelet contains large numbers of granules The cytoplasm may be intensely blue in some instances, probably a sign of immaturity These apparently young forms are associated with states of thrombocytopenia or with the sudden increase in number of platelets following hemorrhage or splenectomy [113]

The size of the platelet varies from the normal to abnormally large forms almost the size of a red cell In normal individuals approximately 82 per cent of the platelets are 2 5 μ in diameter or less [134] In cases of thrombocytosis, the deviation from normal is usually due to an increase of small platelets Increase of large platelets is often associated with intense regenerative activity, abnormal function, or hypoplasia of the megakaryocytes in the bone marrow. Although the total number of platelets is abnormally decreased, large platelets are characteristic of the blood picture in aplastic anemia, untreated pernicious anemia, paroxysmal nocturnal hemoglobinuria, chronic lymphocytic leukemia, acute leukemias, or the acute exacerbation of chronic leukemia [109, 175] Giant platelets are seen in increased numbers in polycythemia vera [123] and in chronic nonleukemic myelosis [25]. Some most unusual forms of platelets have been seen in a few patients with myeloid metaplasia in whom splenectomy had been performed [37].

A decrease in the number of platelets is seen as a result of large doses of benzol, following certain drugs and toxins [58], and following radiation [113] In infections there may be a decrease of platelets followed by a rapid increase [149, 175] It is well known that platelets increase rapidly following hemorrhage [134], splenectomy [106, 110] or other surgical operations, childbirth, and fractures [48, 134]. The number of platelets has been increased to more than $1000 \times 10^3/mm^3$ (normal value, 200 to $400 \times 10^3/mm^3$) following splenectomy for purpura hemorrhagica [77] and after other surgical procedures. Occasionally an increase in platelets has been associated with postoperative thrombosis and pulmonary embolism [48, 109] In myelogenous leukemia, the platelets are frequently normal or increased In seven of 35 cases in one study [124] the platelets were abnormally increased (800 to $2000 \times 10^3/mm^3$) When the platelets are increased there may also be many young and abnormal forms of platelets with fragments of megakaryocytes appearing in the peripheral blood Irradiation of the patient causes a decrease of platelets Marked increase or marked decrease from the usual level of platelets in a patient with myelogenous leukemia is a sign of change in the course of the disease

(*b*) Megakaryocyte (peripheral blood) The megakaryocyte may be seen in the peripheral blood in certain pathologic conditions such as myelogenous leukemia, agnogenic myeloid metaplasia, polycythemia, pneumonia, and sepsis [122] The nucleus is practically all that is seen of this large distorted cell when it reaches the blood stream The diameter of the nucleus may vary from that of a red cell to two or three times that of a monocyte The nucleus of the megakaryocyte has a blue-purple, wavy chromatin structure, with a dark periphery Sometimes there is a folded or lobulated appearance to the chromatin The light-blue cytoplasm is

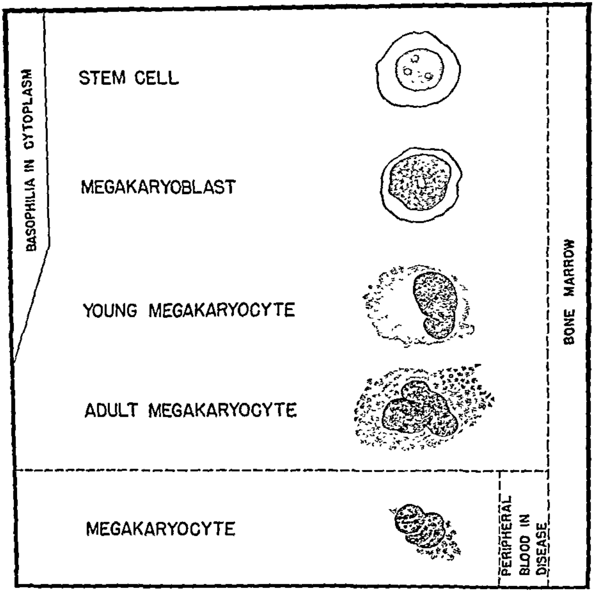

FIG 9 Diagram of the maturation of the thrombocytic series Platelets are shown diagrammatically at the periphery of the megakaryocyte nucleus (Only platelets are seen normally in the peripheral blood)

7. THE PLATELETS AND THE THROMBOCYTIC SERIES

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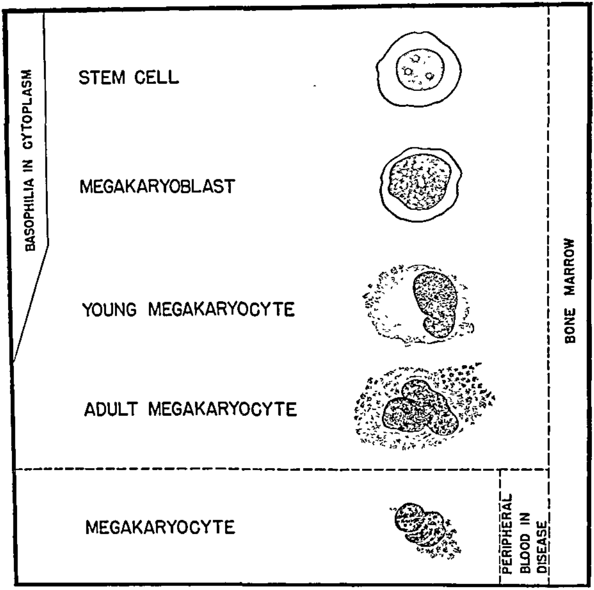


FIG 9 Diagram of the maturation of the thrombocytic series Platelets are shown diagrammatically at the periphery of the megakaryocyte nucleus (Only platelets are seen normally in the peripheral blood)

rarely seen intact, but appears torn and fragmented, usually containing a mass of blue-purple or azurophilic granules Platelets that appear as fragments of this granule-containing cytoplasm are often seen in masses attached to or in the vicinity of the megakaryocyte

(c) MEGAKARYOCYTE (bone marrow) As indicated by its name, the megakaryocyte is the largest cell of the bone-marrow series (20 to 40 μ), but varies widely in size and appearance The nucleus is lobulated and is much more dense and deeper blue-purple than the younger cells of the megakaryocyte series. The cytoplasm varies in color from blue to pink and contains a variable number of characteristic red-purple granules Fragments of cytoplasm are seen breaking off from the cell. Some of these fragments of cytoplasm contain granules and look like platelet material. Platelets are usually associated with these cells

(d) PROMEGAKARYOCYTE (bone marrow). The promegakaryocyte *is smaller than the megakaryocte* The nucleus is round or beginning to be lobulated The cytoplasm is more basophilic than in the older form Granules are present, but are usually fine and scattered around the nucleus

(e) MEGAKARYOBLAST (bone marrow). The megakaryoblast is larger than the other blast forms in the bone marrow, *but smaller than the adult megakaryocyte* The nucleus is slightly irregular and the chromatin is granular but coarser in structure than in the myeloblast. One or more nucleoli are present. The cytoplasm is relatively small in amount and is deeply basophilic

(f) ABNORMAL MEGAKARYOCYTES (bone marrow) Megakaryocytes with multiple nuclei (polykaryocytes) have been shown to be increased in the bone marrow in pernicious anemia before therapy [63] These multinucleated megakaryocytes present many abnormal stages of development There may be hypersegmentation of the nucleus in a cell with basophilic cytoplasm or with mature (pink) cytoplasm In some thrombocytopenias there is a disturbance of the normal maturation of the megakaryocyte with a preponderance of immature forms, while in other types there is a disturbance of function For further information the reader is referred to articles on bone-marrow aspirations [35, 45, 73, 111, 146]

3. *EXAMINATION OF PLATELETS IN THE BLOOD FILM.*

(a) INDIRECT METHOD OF ESTIMATING THE NUMBER OF PLATELETS. The methods of counting platelets are discussed in Unit 6, p 50 of the *Syllabus* The number of platelets can be estimated indirectly by examination of the film of blood stained with Wright's stain to determine semiquantitatively whether the number is increased, normal, or decreased In this procedure the number of platelets is compared to the number of red cells in the film and will be influenced by the red-cell count. For example, if the red-cell count is *5.0×10^6/mm³ and the platelet distribution on the film* appears "normal," this may correspond to an absolute platelet count of 250×10^3/mm³ The same appearance of a "normal" number of platelets relative to the number of red cells on the film may occur in a severe anemia Thus, if the red-cell count is 1.0×10^6/mm³, an apparently "normal" number of platelets may cor*respond to an absolute platelet count of 50×10^3/mm³* This is a significant degree of thrombocytopenia which may be observed in pernicious anemia

(b) CLINICAL SIGNIFICANCE The value of observing the number of platelets in a blood film lies in the detection of an abnormal increase or decrease The absence of platelets in what appears to be a normal film may confirm a *diagnosis of thrombocytopenic purpura* when hemorrhagic symptoms are present The decreased number of platelets in the blood film in the presence of marked red-cell changes may help in classifying the anemia

8. CASE STUDIES OF VARIOUS DISORDERS OF THE BLOOD

In the following sections the plates and data are representative of findings from patients in whom the blood film and laboratory data are of definite diagnostic value. In these sections the morphologic aspects and clinical interpretation are emphasized. For detailed clinical descriptions the reader is referred to M. M. Wintrobe, *Clinical hematology* [186]; for pathologic physiology, to "Disorders of the blood," by W. B. Castle, which appears as chapter 14 in *Pathologic physiology*, edited by W. A. Soderman [27], and also to *Pathological physiology and clinical description of the anemias*, by W. B. Castle and G. R. Minot [29]. The following classification of anemia [29] (*Syllabus*, Unit 14) serves as a guide to the physiologic activity of the bone marrow and indicates the mechanism of the anemia when it is known. The illustrative plates are indicated on the outline.

BONE MARROW PHYSIOLOGICALLY HYPERACTIVE AND ALWAYS HYPERPLASTIC

(1) Acute and subacute blood loss (without iron deficiency)
- (a) Hemorrhage, external (Plate IX, p. 49)
- (b) Hemorrhage, internal

(2) Hemolytic anemias — increased destruction and production of red cells
- (a) Congenital and hereditary defects of red cells
  - Congenital hemolytic jaundice (hereditary spherocytosis) (Plate VII, p. 43)
  - Sickle-cell anemia (Plate VI, p. 41)
  - Sickle-cell trait
  - Cooley's anemia (thalassemia major) (Plate V, p. 37)
  - Cooley's trait (thalassemia minor)
- (b) Acquired defects of red cells
  - Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria
  - Acute hemolysis with thermal burns
- (c) Hemolytic anemias associated with hemolysins
  - Paroxysmal cold hemoglobinuria
  - Hemolysin in acquired hemolytic jaundice
  - Venom poisoning
- (d) Hemolytic anemias associated with abnormal agglutination of red cells
  - Hemolytic transfusion reactions
  - Erythroblastosis fetalis (Plate VIII, p. 47)
  - Acquired hemolytic jaundice
- (e) Infections
  - Oroya fever (Carrion's disease)
  - Malaria
- (f) Chemical intoxication (Plates VII and IX, pp. 43 and 49)
- (g) Unknown mechanisms
  - Favism
  - Anemia in disease of the liver

BONE MARROW PHYSIOLOGICALLY HYPOACTIVE; MARROW MAY BE APLASTIC, HYPOPLASTIC, APPROXIMATELY NORMAL, OR HYPERPLASTIC

(1) Nutritional deficiency
- (a) Deficiency of anti-pernicious anemia principle (Plate III, p. 31)
  - Deficiency of food (extrinsic) factor
  - Deficiency of gastric (intrinsic) factor
  - Intestinal factors
- (b) Deficiency of Will's factor
- (c) Deficiency of iron (Plate IV, p. 35)

(2) Endocrine deficiency

(3) Toxic inhibition of blood production
- (a) External agents
- (b) Internal agents

(4) Physical injury
- (a) Radiation

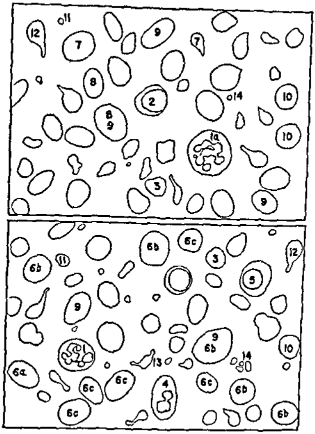
(5) Mechanical interference
- (a) Inadequate marrow capacity
- (b) Myelophthisis (Plates X, XI, XII, XIII, pp. 53, 59, 63, 65)

PLATE III PERNICIOUS ANEMIA

Upper picture: Before treatment (Wright's stain).
Lower picture: Six days after initial treatment with liver extract, showing reticulocytes (stained with brilliant cresyl blue and counterstained with Wright's stain).

Key:

1. Neutrophil
1a Multilobed neutrophil
2. Lymphocyte
3 Normal red cell
4. Normoblast with reticulum
5 Late erythroblast with reticulum
6a Early reticulocyte
6b. Intermediate reticulocyte
6c. Late reticulocyte
7. Stippled cell
8 Polychromatophilic cell
9. Oval macrocyte
10 Round macrocyte
11 Microcyte
12. Tailed or pear-shaped forms
13 Irregular forms
14. Platelets



9. PLATE III. PERNICIOUS ANEMIA

1. *DESCRIPTION OF UPPER PICTURE: BEFORE TREATMENT (WRIGHT'S STAIN).* This is definitely the picture of a macrocytic anemia because the average diameter of the red cells is greater than normal (compare with normal cells (*3*) and see also Fig 1 and Plates I and II) As inspection shows, the variation in size is extreme, from the tiny microcytes (*11*) to oval macrocytes (*9*), the variation in size may be measured according to the method of Price-Jones [144] as shown in Table 1 and Fig 3 There is marked variation in shape, with many irregular forms (*13*), the most characteristic type being the pear-shaped or tailed forms (*12*) Most of the cells are well filled with hemoglobin, as judged by the depth of staining A few of the small cells are definitely hypochromic (pale-staining). Polychromatophilic cells (*8*) and stippled cells (*7*) are present Note that the stippled cells are stained by using Wright's stain alone and are not to be confused with reticulocytes (see lower picture)

There are two white cells in the field—a typical small lymphocyte (*2*) and an abnormally large multilobed neutrophil (*1a*) The platelets (*14*) occur singly and are definitely decreased in number

2. *DESCRIPTION OF LOWER PICTURE SIX DAYS AFTER INITIAL TREATMENT WITH LIVER EXTRACT* The film is stained with brilliant cresyl blue to show the reticulocytes and counterstained with Wright's stain In this picture the red cells show the same degrees of macrocytosis and variation in size and shape as in the upper picture, before treatment. The hemoglobin content of the red cells in the lower picture is more variable than in the upper picture, as is evidenced by the variable intensity of staining This is especially noticeable in the macrocytic reticulocytes, which are sometimes less densely stained than many of the nonreticulated red cells The red cells containing a network of blue-staining reticulum (*6a, 6b, 6c*) are the reticulocytes The reticulocytes are numerous, and their age (in the peripheral blood) can be estimated roughly by the amount of reticulum contained in the cells. Thus, a large amount of reticulum (*6a*) indicates a very young cell As the cell matures the amount of reticulum decreases (*6b*) until there are only traces of it remaining (*6c*) The normoblast (*4*) and erythroblast (*5*) are immature nucleated forms of the erythrocytic series that contain reticulum and should be counted

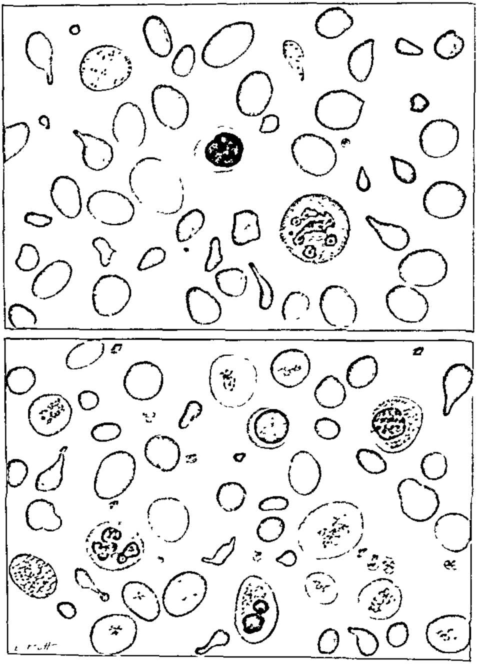


PLATE III. PERNICIOUS ANEMIA

TABLE 4 LABORATORY DATA FOR PLATE III

Observations	Before *treatment* (upper picture)	Six days after initial treatment (lower picture)
Red-cell count ($10^6/mm^3$)	*1 16*	*1 25*
Hemoglobin (gm/100 ml)	4 6	4 7
Hematocrit (percent)	14 5	15 8
Red-cell indices·		
MCV [mean corpuscular volume (μ^3)]	125	127
MCHC [mean corpuscular hemoglobin concentration (gm/100 ml)]	32	29
MCH [mean corpuscular hemoglobin ($\mu\mu g$)]	39	38
Reticulocytes (percent)	1 0	21
White-cell count ($10^3/mm^3$)	2 0	5 4
Platelet count ($10^3/mm^3$)	95 0	210 0
Icterus index (units)	15	5

both as reticulocytes and as nucleated red cells (see Plate I).

The white cells in the lower drawing include a normal lymphocyte (*2*) and a normal neutrophil (*1*). The platelets are plentiful

3. *INTERPRETATION OF BOTH PICTURES.* The marked macrocytosis and extreme variation in size of the red cells are consistent with the diagnosis of pernicious anemia in relapse, in which the variation in size *is greater than in any other macrocytic anemia* [39] Among the macrocytes can be seen many oval macrocytes (*9*) that are well filled with hemoglobin These are especially characteristic of pernicious anemia and are present in large numbers when the red-cell count is very low

Well-formed microcytes (*11*), full of hemoglobin, and tailed or pear-shaped *forms (12) are also characteristic* of this disease The number of polychromatophilic red [illegible] and nucleated red cells in untreated [illegible] 4 days and [illegible] 's following effective therapy (lower picture) or in spontaneous remission, which rarely occurs Stippled cells are common, as *they are in many severe anemias* Cabot rings and Howell-Jolly bodies in the red cells are found frequently (not illustrated in these pictures; see Plates I and V).

Before therapy the neutrophils are decreased in number and many of them are abnormally large cells with multilobed nuclei, which are referred to as multilobed neutrophils or "macropolys" Because of the decreased number of neutrophils, lymphocytes appear to be increased, although their absolute number is within normal limits; this is known as relative lymphocytosis (*Syllabus, Unit 15,* p *198)* After effective therapy, the neutrophils quickly return to normal in appearance and in number.

Before therapy the platelets *are single, large, and decreased* in absolute number; they return to normal following treatment.

When the anemia is severe (red-cell count 0 5 to $2\,0 \times 10^6/mm^3$), these abnormal red-cell characteristics are striking, and study of the blood film is of great diagnostic value However, when the anemia is less *severe (red-cell count 2 0 to $3\,0 \times 10^6/mm^3$), these* features are present to a lesser degree, and the diagnosis is more difficult (*Syllabus,* Unit 14, Table 9, p 182). At higher levels of the red-cell count (above $3.0 \times 10^6/mm^3$), some of the abnormal features, such as oval macrocytes, microcytes, tailed forms, stippling, large platelets, and multilobed neutrophils, may be present, but in decreased numbers

The macrocytosis and the degree of variation in size of red cells are more striking in Addisonian pernicious anemia than in the other macrocytic anemias that respond to liver extracts, folic acid, and vitamin B_{12} such as the macrocytic anemias of pregnancy and those of nutritional (extrinsic-factor) deficiency [39]

In the hemolytic anemias, there may be marked macrocytosis and considerable (but not extreme) variation in the size of the red cells in such conditions as severe *and chronic acquired hemolytic jaundice,* acute exacerbations of chronic hemolytic jaundice, and paroxysmal nocturnal hemoglobinuria. In these conditions, however, without any treatment, the blood film shows marked polychromatophilia (with Wright's stain) and reticulocytosis (with brilliant cresyl blue), as shown in Plate VII. The macrocytes are round and many are poly*chromatophilic Oval macrocytes are seldom* seen in these hemolytic anemias The platelets and granulocytes are usually normal and not decreased as in pernicious anemia, except in paroxysmal hemoglobinuria of the nocturnal type

In certain macrocytic anemias that are "refractory" to liver extract and result from decreased production of red cells, there may occasionally be moderate to marked macrocytosis This may occur in myelophthisic anemia due to leukemia and in the anemias associated with azotemia and chronic liver disease In these conditions, the variation in size of red cells is moderate and the number of reticulocytes is low compared to that of the hemolytic anemias.

10. PLATE IV. HYPOCHROMIC ANEMIA (Iron-deficiency Anemia)

1 *DESCRIPTION OF UPPER PICTURE MODERATE HYPOCHROMIC ANEMIA IN A 17-YEAR-OLD GIRL.* This is the picture of a moderate microcytic anemia with many red cells that are slightly smaller in diameter than the normal cells (*4*). There is moderate variation in shape with a few elongated (pencil) forms (*7*) and a few irregular forms. Microcytes (*6*) are present and one polychromatophilic cell (*9*). The hemoglobin concentration of the red cells is slightly below normal. This may best be judged by comparing the intensity of staining with that of a group of normal red cells as seen in Plate I.

The white cells are normal and include a small lymphocyte (*2*) and a neutrophil (*1*). The platelets (*13*) are normal in number.

2. *DESCRIPTION OF LOWER PICTURE: SEVERE HYPOCHROMIC ANEMIA FROM CHRONIC BLOOD LOSS (HEMORRHOIDS) IN A 62-YEAR-OLD MAN.* Many of the red cells in this drawing are microcytic and hypochromic. However, the variation in size here is extreme, from two large target cells (*8*), which are probably thin cells, to small microcytes (*6*). Also, the variation in shape is extreme, as evidenced by the many irregularly shaped cells and some pencil forms. Polychromatophilic cells (*9*), a normoblast (*11*), and a stippled cell (*10*) are present. Most of the red cells are definitely hypochromic, or low in hemoglobin concentration, as indicated by the pallor of the cells. The hemoglobin appears to be concentrated about the periphery of these thin cells, so that the color seems to decrease gradually from the periphery toward the center. These progressive changes are in contrast to the sharply defined, punched-out areas of central pallor that appear to result from artifacts in fixation or staining of the film.

Two normal white cells are shown in this picture: a neutrophil (*1*) and a monocyte (*3*). The platelets are large and abnormal in shape, as often occurs in a severe anemia, especially of a chronic type. They appear to be approximately normal in number, relative to the red cells on the film, but the platelets may be decreased in absolute number, since the red-cell count is low (*Syllabus*, Unit 7, p. 61).

3 *INTERPRETATION OF BOTH PICTURES* The contrast between these two blood films is so extreme that it suggests different disease processes. However, both represent different degrees of chronic hypochromic microcytic anemia due to iron deficiency. In chronic hypochromic anemia, the greater the anemia, or the lower the hemoglobin concentrations, the more abnormal is the appearance of the red cells.

The upper picture is typical of the changes occurring in the many instances of mild hypochromic anemia. Since the morphologic changes are subtle, the condition may be overlooked. The direct comparison of the patient's blood film with that of a normal person will aid materially in detection of moderate changes (*Syllabus*, Unit 7, p. 59). Also, unless the red cells are well separated on the blood film and well stained, the moderate changes may be missed. However, the lower picture represents extreme changes in the red cells, resulting from chronic iron deficiency due to blood loss over many years.

Usually there is little difficulty in making a correct diagnosis of hypochromic anemia in such cases as those shown here, if the appearance of the blood film is correlated with the red-cell indices and the reticulocyte count. Thus, in both of these cases the values for mean corpuscular volume, MCV, indicate microcytosis and those for mean corpuscular hemoglobin concentration, MCHC, indicate hypochromia. The variation in the diameters is extreme in the lower picture. In both of these cases, the reticulocytes are significantly few, indicating decreased production of red cells by the bone marrow. The level of reticulocytes is lower than would occur in hemolytic anemias, including Cooley's anemia.

TABLE 5 LABORATORY DATA FOR PLATES IV AND V

Observations	Hypochromic anemia Plate IV		Cooley's anemia Plate V
	Upper picture	Lower picture	
Red-cell count (10^6/mm³)	5.1	1.2	3.3
Hemoglobin (gm/100 ml)	9.2	2.0	5.8
Hematocrit (percent)	32.0	7.8	25.0
Red-cell indices			
MCV [mean corpuscular volume (μ^3)]	62	65	76
MCHC [(mean corpuscular hemoglobin concentration (gm/100 ml)]	29	26	23
MCH [mean corpuscular hemoglobin ($\mu\mu$g)]	18	17	17
Reticulocytes (percent)	2	2	6.6
Platelet count (10^3/mm³)	250	200	
White-cell count (10^3/mm³)	10.6	7.6	4.4
Icterus index (units)	14	2	10

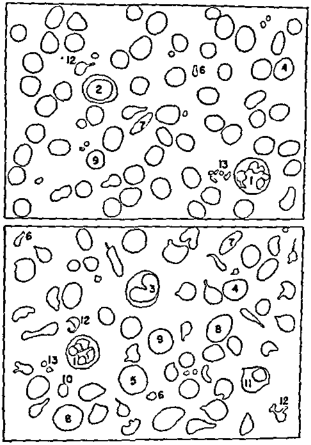
PLATE IV. HYPOCHROMIC ANEMIA

Upper picture. Moderate hypochromic anemia in a 17-year-old girl, before treatment

Lower picture: Severe hypochromic anemia from chronic blood loss (hemorrhoids) in a 62-year-old man, before treatment

Key:

1. Neutrophil
2. Small lymphocyte
3. Monocyte
4. Normal red cell
5. Macrocyte
6. Microcyte
7. Pencil form
8. Target form
9. Polychromatophilic cell
10. Stippled microcyte
11. Normoblast
12. Irregular forms
13. Platelets



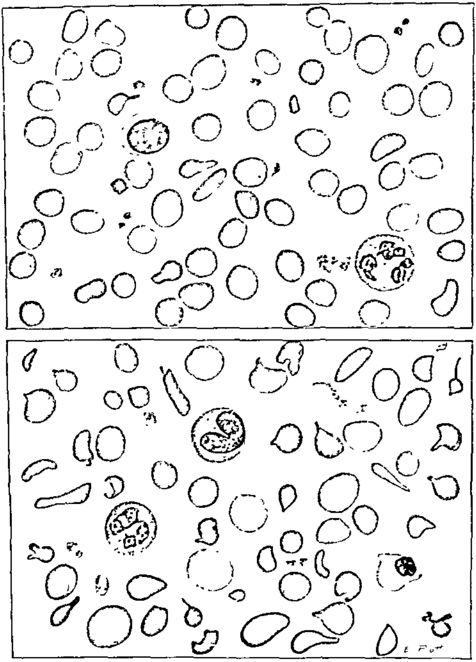


PLATE IV. HYPOCHROMIC ANEMIA

PLATE V. COOLEY'S ANEMIA

Key.

1. Neutrophil
2. Young lymphocyte
3. Myelocyte
4. Normal red cell
5. Macrocyte
6. Microcyte
7. Pencil form
8. Target form
9. Polychromatophilic red cell
10. Stippled cell
11. Cabot ring form
12. Red cell with Howell-Jolly body
13. Normoblast
14. Late erythroblast
15. Early erythroblast
16. Irregular forms
17. Platelets

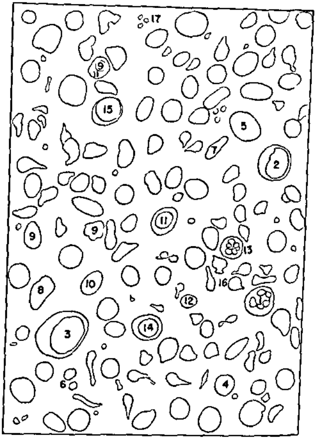


TABLE 6 THE INHERITANCE OF COOLEY'S TRAIT AND COOLEY'S ANEMIA (Courtesy of M B Strauss)

Abnormal gene associated with Cooley's disease = C
Normal gene (allelomorph) = *c*

Phenotype	*Genotype*
Normal	*cc*
Cooley's trait	*Cc*
Cooley's anemia	*CC*

Possible genetic combination of inheritance

Parents	*Possible children*	*Ratio*
Cc × *cc*	*Cc*, *cc*	1 1
Cc × *Cc*	*CC*, *Cc*, *cc*	1 2 1
CC × *cc*	*Cc*	All
CC × *Cc*	*CC*, *Cc*	1 1

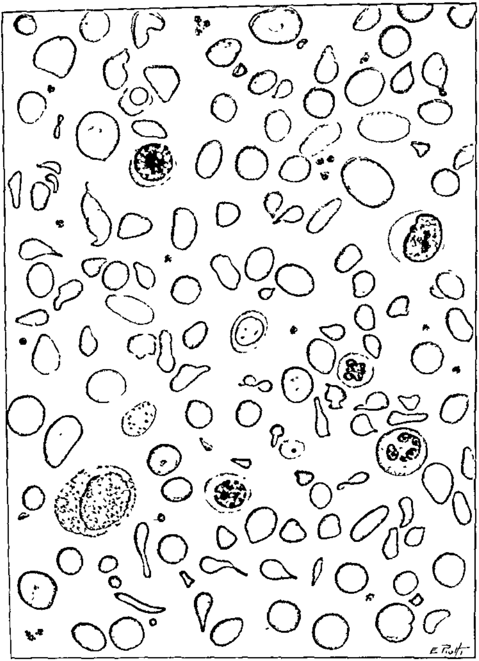


PLATE V. COOLEY'S ANEMIA

11. PLATE V. COOLEY'S ANEMIA (Thalassemia Major, Mediterranean Anemia)

1. *DESCRIPTION.* In this picture the red cells show extreme variation in size, shape, and *hemoglobin content* A few red cells appear to be normal in size (*4*), but the majority are microcytes. The single most striking feature of the erythrocytes is their extreme variation in shape, which exceeds that usually found in severe anemias and includes many bizarre shapes Because of the marked variation in the hemoglobin content of cells, there is a marked variation in the intensity of staining of these cells A few cells appear well filled with hemoglobin, but *most of them have a decreased amount of* hemoglobin which appears to be distributed around the edge of the cell, as evidenced by the concentration of stained material, such as is seen in hypochromic anemia (Plate IV). Many target forms (*8*) [176] are present Polychromatophilic cells (*9*) and nucleated red cells are increased A normoblast with a multilobed nucleus (*13*), a late erythroblast (*14*), and an early erythroblast (*15*) are shown. Cells with Cabot rings (*11*), stippling (*10*), *and Howell-Jolly bodies (12) are present.*

Immature leukocytes include a myelocyte (*3*) and a young lymphocyte (*2*). The platelets (*17*) appear to be normal

2. *INTERPRETATION.*

(*a*) Cooley's Anemia This blood film is from a 5-year-old child of Italian parentage, who showed increased fatigability, pallor, recurrent attacks of abdominal pain, mongoloid facies, enlargement of the liver and *spleen, and acholuric jaundice.*

The changes in the red cells in this picture do not differ greatly (except for the presence of polychromatophilic cells — elevated reticulocytes) from those of severe hypochromic anemia, as seen in the lower picture of Plate IV. From the blood films alone these two conditions may not be distinguishable However, it is important to recognize, from the data given in Table 5, that the marked changes in red cells occur at a high level of the red-cell count, $3\ 3 \times 10^6/\text{mm}^3$, and at a hemoglobin concentration of 5 8 gm/100 ml Conversely, in the severe hypochromic anemia with comparable red-cell changes, the red-cell count is markedly low, $1\ 2 \times 10^6/\text{mm}^3$, and the hemoglobin concentration *is excessively low, 2 0 gm/100 ml* *In Cooley's anemia,* the absolute number of reticulocytes is consistently elevated above normal, while in severe hypochromic anemia, *untreated, the absolute number of reticulocytes* is decreased below normal [19, 182].

This blood film might be confused with that of pernicious anemia because of the marked variation in shape of cells However, it should be reemphasized that the red cells in Cooley's anemia are hypochromic and microcytic, whereas those of pernicious anemia are normochromic and macrocytic.

(*b*) Cooley's Trait The blood picture in Cooley's *trait is similar to that of a mild hypochromic anemia,* showing microcytosis, hypochromia, and moderate variation in size and shape In addition, there are pencil forms, target forms, frequent stippled cells, rare nucleated red cells, and fewer than 4 percent of reticulocytes. The red-cell count varies from 5 0 to $8\ 0 \times 10^6/\text{mm}^3$, and the mean corpuscular volume is definitely below normal A comparison of the blood picture of Cooley's anemia with that of Cooley's trait *may well be made by studying Plate IV (hypochromic* anemia of iron deficiency), assuming that the red-cell counts are about $5 \times 10^6/\text{mm}^3$ in both instances The final diagnosis depends on the lack of response to iron therapy and a careful study of the blood in other members of the family Clinically, the subjects with Cooley's trait are usually in normal health, and it is only by careful laboratory studies that the presence of the trait is found A comparison of the clinical and hematologic findings is given in the report by Daland and Strauss [40]

(*c*) Genetics of Cooley's Anemia and Cooley's Trait (Table 6) The genetic relation and clinical differentiation of Cooley's anemia and Cooley's trait have *been reported by several investigators [24, 40, 43, 44,* 117, 133, 177, 187] There is evidence for at least two possible explanations of the inheritance two nonallelomorphic dominant factors, one inherited from each parent, would result in Cooley's anemia; or there may be a single "incomplete" dominant factor in which the heterozygote would exhibit the Cooley's trait and the homozygote, the Cooley's anemia. The trait is found more frequently since the characteristic changes in the red cells have been more generally recognized

12. PLATE VI. SICKLE-CELL ANEMIA

1. *DESCRIPTION OF UPPER PICTURE* (unmanipulated film of peripheral blood from a 13-year-old Negro girl) The red cells in this film of peripheral blood show more than normal variation in size. Many of the red cells appear to be a little larger than normal [49] and show more than normal variation in shape, with microcytes, polychromatophilic macrocytes (*5*), and target cells (*6*). The number of crescent or elliptic forms (*7*) and oat-shaped forms is striking; these cells probably represent irreversible sickled forms [161] that have lost their filamentous processes There is marked variation in hemoglobin content, as manifested by the variation in intensity of staining The presence of many target cells, which are large thin cells, gives the appearance of a lowered hemoglobin content, although the mean corpuscular hemoglobin concentration (MCHC) is only slightly reduced The nucleated red cells, which in this film are normoblasts (*8*) and late erythroblasts (*9*), appear in a crisis in sickle-cell disease or may be present in the blood in patients showing chronic anemia of moderate severity

Only one white cell, a normal lymphocyte (*2*), is shown Platelets appear to be normal

2 *DESCRIPTION OF LOWER PICTURE* (film of reduced, anoxic venous blood from a 22-year-old Negro male) Venous blood was reduced by equilibration with 90 percent of nitrogen and 10 percent of carbon dioxide to remove oxygen from the hemoglobin and produce sickling The film was then made and allowed to dry in a chamber containing the same gas mixture to maintain the hemoglobin in the anoxic form When a blood film is dried in room air, the sickled forms are well oxygenated and revert to a normal shape The sickled forms (*7*), *stained with Wright's stain, exhibit the great variety* of filamentous processes that are seen in unstained wet preparations of blood in which the hemoglobin is reduced by the use of reducing agents such as sodium metabisulfite, ascorbic acid [38], or hydrogen sulfide [172], or when the oxygen is removed by equilibration with carbon dioxide, or by incubation in a sealed wet preparation for 10 to 24 hours. It is interesting to note that the normoblasts (*8*) and the polychromatophilic cells are sickled (*5*)

The platelets appear to be normal in this film, and one normal neutrophil (*1*) is seen Obviously, the only cells that sickle are those containing hemoglobin of the abnormal variety found in patients with sickle-cell trait or anemia [140]

3 *INTERPRETATION OF BOTH PICTURES.* The upper picture is from a blood film from a Negro girl who has maintained a red-cell count of 2 0 to 3 5 $\times 10^6/mm^3$, a hemoglobin level of 6 2 to 9 4 gm/100 ml, and reticulocytosis during a period of nine years of observation. On many occasions, an acute crisis with increased anemia and muscle pains has been precipitated by slight infections Otherwise, the patient has maintained fairly normal health

The lower picture is from a Negro male who has maintained a red-cell count of 4 0 to 5 4 $\times 10^6/mm^3$, a hemoglobin level of 9 5 to 12 6 gm/100 ml, and reticulocytosis during a period of eight years of observation

In many cases of sickle-cell anemia, as opposed to the sickle-cell trait, the diagnosis can be suspected from observation of a film of peripheral blood for the presence of sickled, oat-shaped, target, and polychromatophilic forms, together with nucleated red cells In some cases of sickle-cell anemia, and in most cases of sickle-cell trait, no definite evidence of the disease is seen in the smear All Negroes should have a test for sickling of the red cells, preferably using sodium metabisulfite (*Syllabus*, Unit 14, p 161) Since sickle-cell disease may occur in the white race [82], any patient with hemolytic anemia should be tested for the sickle-cell phenomenon

4 *GENETICS* Neel [132] has demonstrated that patients with the sickle-cell trait are heterozygous "carriers" of an abnormality which occurs without symptoms in from 4 to 11 percent of Negroes Pauling *et al* [140] have demonstrated that patients with the sickle-cell trait have a *mixture* (Ss) of normal and abnormal (sickling) hemoglobin that requires a low oxygen tension to sickle Hemoglobin of a normal individual would *be represented as ss However, patients with sickle-cell* anemia are homozygous (SS) and have 100-percent abnormal (sickling) hemoglobin in blood which sickles more completely at a higher oxygen tension [162] than does the blood (mixture) from the sickle-cell trait The ratio among Negroes of those with the sickle-cell trait (heterozygous) to those with sickle-cell anemia (homozygous) is approximately 40 1 [140] Patients with sickling of the red cells may be classified as having the sickle-cell trait, if there is no anemia, and sickle-cell anemia, if a hemolytic anemia is present The inheritance may then be identical to that of Cooley's trait (*Cc*) and Cooley's anemia (*CC*), as indicated for Cooley's abnormality in Table 6

PLATE VI. SICKLE-CELL ANEMIA

Upper picture: Unmanipulated film of peripheral blood from a Negro girl

Lower picture: Film of reduced (anoxic) venous blood from a Negro male

Key:

1 Neutrophil
2 Lymphocyte
3 Normal red cell
4 Macrocyte
5. Polychromatophilic cell
6 Target form
7. Sickled cells
8 Normoblast
9 Late erythroblast
10 Platelets

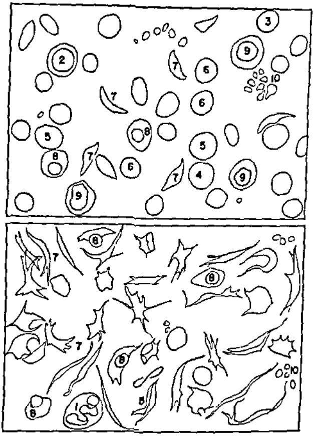


TABLE 7. LABORATORY DATA FOR PLATE VI

Observations	Upper picture	Lower picture
Red-cell count (10^6/mm^3)	2.9	4.3
Hemoglobin (gm/100 ml)	7.9	9.4
Hematocrit (percent)	23.4	30.5
Red-cell indices		
MCV [mean corpuscular volume (μ^3)]	81	71
MCHC [mean corpuscular hemoglobin concentration (gm/100 ml)]	34	31
MCH [mean corpuscular hemoglobin ($\mu\mu$g)]	27	22
Reticulocytes (percent)	6	5
Nucleated red cells (per 100 white cells)	5	0
White-cell count (10^3/mm^3)	12	14.5
Icterus index (units)	15	12

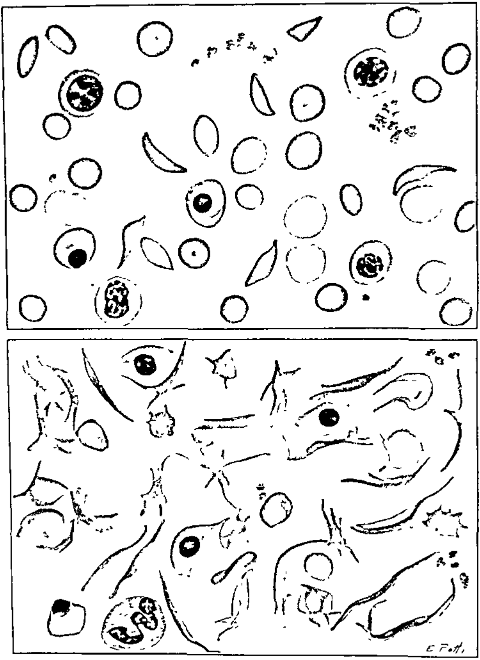


PLATE VI SICKLE CELL ANEMIA

PLATE VII HEMOLYTIC ANEMIA — CHRONIC AND ACUTE

Upper pictures: Chronic hemolytic jaundice — Hereditary spherocytosis (*two films from the same sample of blood; left,* Wright's stain, *right,* stained with brilliant cresyl blue and Wright's stain)

Lower picture: Acute hemolytic anemia following sulfanilamide therapy (Wright's stain).

Key:

1 Neutrophil
2. Young neutrophil (band)
3 Metamyelocyte
4 Myelocyte
5. Eosinophil
6. Monocyte
7. Small lymphocyte
8 Normal red cell
9 Spherocyte
10 Polychromatophilic cell
11 Reticulocyte
12 Macrocyte
13 Irregular red cell (lunar)
14 Normoblast
15 Late erythroblast
16 Platelets

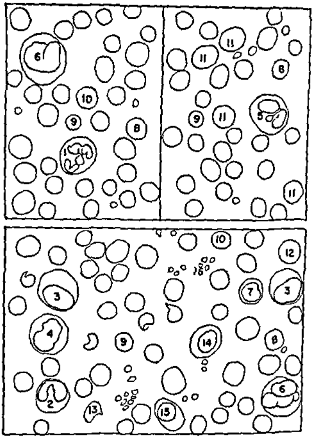


TABLE 8 LABORATORY DATA FOR PLATE VII

Observations	Chronic hemolytic jaundice (upper pictures)	Acute hemolytic anemia (lower picture)
Red-cell count (10^6/mm^3)	4.5	1.4
Hemoglobin (gm/100 ml)	12.0	4.6
Hematocrit (percent)	34.6	15.5
Red-cell indices		
MCV [mean corpuscular volume (μ^3)]	77	111
MCHC [mean corpuscular hemoglobin concentration (gm/100 ml)]	35	30
MCH [mean corpuscular hemoglobin ($\mu\mu$g)]	26	33
Reticulocytes (percent)	10.9	8.4
Osmotic fragility of red cells	Moderate increase	Marked increase
Spherocytes in blood film	Present	Present
White-cell count (10^3/mm^3)	11.6	54.0
Plasma bilirubin (mg/100 ml)	4.0	2.7
Plasma hemoglobin (mg/100 ml)	0	160
Bilirubinuria	0	0
Hemoglobinuria	0	Marked

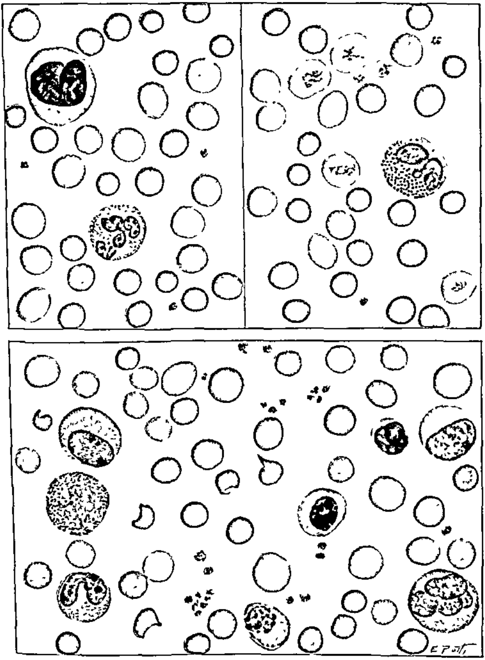


PLATE VII HEMOLYTIC ANEMIA—CHRONIC AND ACUTE

13. PLATE VII. HEMOLYTIC ANEMIA — CHRONIC AND ACUTE

1. *UPPER PICTURE: CHRONIC HEMOLYTIC JAUNDICE — HEREDITARY SPHEROCYTOSIS* (Two films from the same sample of blood. The *left-hand* film is stained with Wright's stain; the *right-hand* film is stained with brilliant cresyl blue and counter-stained with Wright's stain)

(*a*) DESCRIPTION. The red cells show moderate variation in size although the average size is about normal This variation in size results from the presence of three types of cells: normal red cells (*8*) spherocytes (*9*), and large polychromatophilic cells (*10*) in the left-hand and reticulocytes (*11*) in the right-hand pictures The spherocytes are small, round, and intensely stained, and are characteristic of this disease, which is also called hereditary spherocytosis The variation in intensity of staining is the striking feature in these two films The larger cells that are polychromatophilic (*10*) and the reticulocytes (*11*) are slightly less intensely stained than the normal cells (*8*), as is often the case with these newly formed cells The spheroidal cells, because of their increased thickness, appear to be abnormally full of hemoglobin, in contrast with the normal cell which shows normal central pallor because of its biconcavity (*Syllabus*, Unit 7, p 60)

Normal white cells are present, namely, monocytes (*6*), neutrophils (*1*), and eosinophils (*5*). The platelets appear normal

(*b*) CLINICAL DISCUSSION These blood films were obtained from a patient with typical congenital hemolytic jaundice who refused splenectomy He has been under observation for 20 years with chronic anemia and reticulocytosis Except for four episodes of biliary obstruction when jaundice was intense with bilirubinuria, the patient has had moderate icterus and acholuria His red-cell count has varied from 3 0 to 4 5 $\times 10^6$/mm³, and his hemoglobin from 7 8 gm to 10 9 gm/100 ml The reticulocytes have fluctuated between 5 and 20 percent The osmotic and mechanical fragilities of the red cells have been increased Similar findings should also be manifest in at least some members of the patient's family

2 *LOWER PICTURE ACUTE HEMOLYTIC ANEMIA — SULFANILAMIDE INTOXICATION* (with leukemoid reaction)

(*a*) DESCRIPTION The red cells show more variation in size than in the upper drawings Polychromatophilic macrocytes (*10*), spherocytes (*9*), and normal cells (*8*) are present In addition, there are irregular forms (*13*) and nucleated red cells — normoblast (*14*) and late erythroblast (*15*) In addition to the appearance of young red cells in this film, there are immature white cells of the granulocyte series — band neutrophil (*2*), metamyelocyte (*3*), and myelocyte (*4*) A normal monocyte (*6*) and a small lymphocyte (*7*) are also present. The platelets are increased in number

(*b*) CLINICAL DISCUSSION. The lower picture was obtained from the blood film of a 23-year-old man, who, because of scarlet fever, was treated with sulfanilamide for only 3 days. On the fourth day, the patient had marked hemoglobinemia and hemoglobinuria, with a decrease in red-cell count to 1 3 $\times 10^6$/mm³ and in hemoglobin to 4 4 gm/100 ml There was an increase in the white-cell count to 54 $\times 10^3$/mm³, with a myeloid response of the granulocytic series and an increase in immature forms of the erythrocytic series appearing in the peripheral blood There was an increase of reticulocytes to 8 4 percent, an increased mean corpuscular volume (111 μ^3), and increase in the osmotic fragility of the red cells The icterus index could not be read because of hemoglobinemia, but the bilirubin was elevated, as shown in Table 8 The number of nucleated red cells increased to 10 per 100 white cells Howell-Jolly bodies and stippled cells, though not shown in the plate, were present, as well as the polychromatophilic cells

The patient recovered promptly, after transfusions, from this fulminating episode of hemolytic anemia, which was characterized by intravascular hemolysis, increased osmotic fragility of the red cells, and a marked physiologic response of the bone marrow The relation of sulfanilamide to hemolytic anemia is discussed in the *Syllabus*, Unit 14, p 180

3 *INTERPRETATION*. The blood pictures in these two hemolytic anemias have a great deal in common In both conditions the peripheral blood shows polychromatophilic cells (or, when vitally stained, reticulocytes), normal cells, and spherocytes Both cases had an increased osmotic fragility of the red cells consistent with the presence of spherocytes In one patient, there was abnormal icterus (bilirubinemia), in the other, hemoglobinemia and hemoglobinuria

The blood picture in the acute hemolytic anemia is more abnormal than in the chronic hemolytic jaundice, as evidenced by the myeloid reaction of the bone marrow, the nucleated red cells, and the fragmented red cells or half-moon shapes Such a striking change in blood picture may also be seen in acute hemolytic anemia resulting from a variety of causes such as naphthalene poisoning [193], thermal burns, hemolytic transfusion reactions, or acquired hemolytic jaundice

14. PLATE VIII. ERYTHROBLASTOSIS FETALIS

1. *DESCRIPTION* The red cells in this film are definitely macrocytic, with some variation in size but *very little variation in shape The macrocytes, whether* mature forms or immature forms, are round (compare with the oval macrocytes in pernicious anemia, Plate III) The cells are well filled with hemoglobin There are many polychromatophilic cells (*8*), nucleated red cells of all stages (*11–15*), stippled cells (*9*), and Howell-Jolly bodies (*10*). Young cells of the granulocytic *series (2, 4) are present in addition to the normal* neutrophil (*1*) and lymphocyte (*3*). Platelets appear to be about normal in number and size

2 *INTERPRETATION* This blood film is from a newborn infant who died of erythroblastosis fe-

TABLE 9 LABORATORY DATA ON ONE NORMAL BABY AT BIRTH AND THREE CASES OF ERYTHROBLASTOSIS FETALIS (Data are not given for the blood film in Plate VIII)

Observations	Normal baby at birth	Erythroblastosis fetalis		
		Baby D, 10 hr	Baby T, 48 hr	Baby K, 10 hr
Red cell count (10^6/mm³)	4 8	4 6	4 4	3 0
Hemoglobin (gm/100 ml)	17 0	15 6	13 3	13 0
Hematocrit (percent)	53 5	53 1	40	43 4
Red-cell indices				
MCV [mean corpuscular volume (μ^3)]	110	114	91	145
MCHC [mean corpuscular hemoglobin concentration (gm/100 ml)]	32	29	33	30
MCH [mean corpuscular hemoglobin ($\mu\mu g$)]	35	34	30	43
Reticulocytes (percent)	1 9	6 3	11	21
Nucleated red cells (per 100 white cells)	1	11	3	53 *
(per mm³)		2134		48,000
Icterus index (units)	—	30	200+	225
White-cell count (10^3/mm³)				
Uncorrected for nucleated red cells	9 6	19 4	8 4	54
Differential white count				
Neutrophils, adult	38	54	54	16
Neutrophils, band	5	23	21	32
Eosinophils	2	1	1	1
Basophils			1	
Metamyelocytes		3		4
Myelocytes	2	2	6	13
Myeloblasts				20
Lymphocytes, small	31	6	8	6
Lymphocytes, large	1	4	3	1
Lymphocytes, young			1	
Lymphocytes, atypical		1		
Monocytes, adult	14	6	5	6
Monocytes, young	7			
Histiocytes				1
Platelet count (10^3/mm³)	150–250	N		77 0
Bleeding time (min)				7 5
Prothrombin (percent normal)				50
Blood group		A Rh+	O Rh+	O Rh+

* The nucleated red cells seen while counting 200 white cells included 40 normoblasts, 12 erythroblasts, and 1 proerythroblast

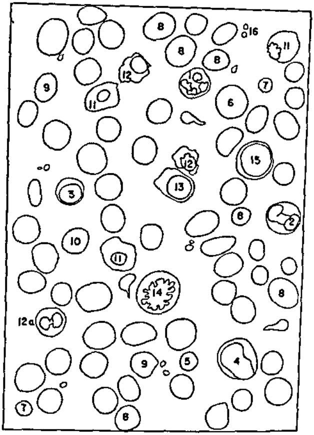


PLATE VIII ERYTHROBLASTOSIS FETALIS

Key:

1. Neutrophil
2. Young neutrophil (band)
3. Small lymphocyte
4. Myelocyte
5. Normal red cell
6. Macrocyte
7. Microcyte
8. Polychromatophilic cell
9. Stippled cell
10. Howell-Jolly bodies
11. Normoblast
12. Late erythroblast

12a Late erythroblast with double nucleus

13. Early erythroblast
14. Erythroblast with nucleus in mitosis
15. Proerythroblast
16. Platelets

talis 16 hours after birth The red-cell count was 1 5 $\times$ 10^6/mm^3, the hemoglobin, 6 2 gm/100 ml The spleen and liver were markedly enlarged The infant's Rh-positive red cells were sensitized by anti-Rh antibody from the mother (*Syllabus*, Unit 12, p 116) In this particular family, there was a classic incidence of erythroblastosis fetalis with death of four infants — all but the first child This indicates that the paternal blood group was homozygous Rh positive

This blood picture can be differentiated morphologically from other macrocytic anemias, because there is more variation in size here than in any other of the anemias except possibly pernicious anemia The picture is *not* characteristic of pernicious anemia, because the macrocytes are not oval, there is comparatively little variation in shape, and there is much more polychromatophilia than is seen in untreated pernicious anemia

The presence of many polychromatophilic cells and nucleated red cells is consistent with the physiologic response of the bone marrow in subacute or chronic hemolytic anemia An acute hemolytic anemia does not usually show such a marked macrocytosis (compare Tables 8 and 9) However, the red cells in the newborn infant are normally macrocytic, are well filled with hemoglobin [130], and show moderate polychromatophilia The mean red-cell diameter in the normal infant is 8 6 μ The macrocytosis and reticulocytosis or erythroblastosis due to the hemolytic reaction are added, therefore, to the normal macrocytosis of the infant's blood cells In addition, in an infant or child, because of the large volume of active bone marrow, any extra demand on the marrow readily produces immature cells of the erythrocytic and granulocytic series that appear in the peripheral blood

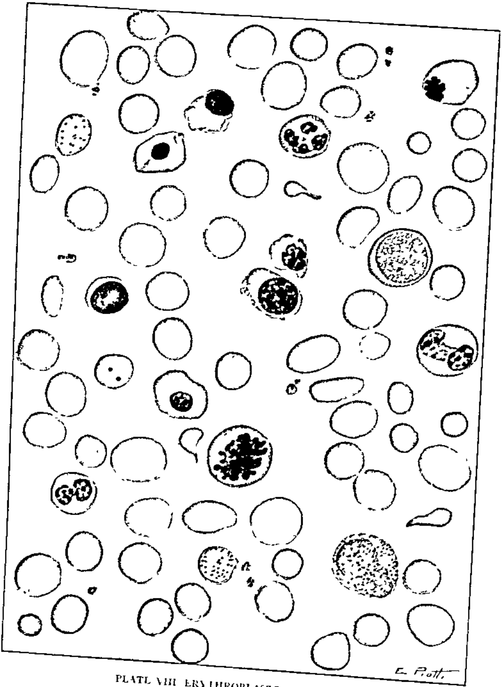


PLATE VIII ERYTHROBLASTOSIS FETALIS

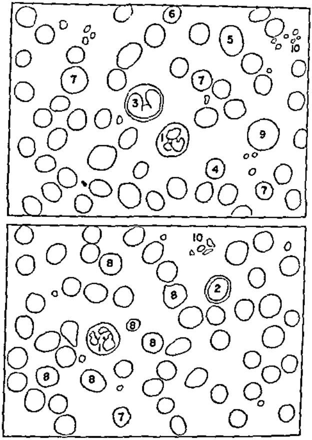


PLATE IX. ACUTE BLOOD LOSS, CHRONIC LEAD POISONING

Upper picture: Acute blood loss
Lower picture: Chronic lead poisoning

Key:
1 Neutrophil
2 Lymphocyte, small
3 Monocyte
4 Normal red cell
5. Macrocyte
6 Microcyte
7 Polychromatophilic red cell
8 Stippled red cell
9. Target form
10 Platelets

TABLE 10 LABORATORY DATA FOR PLATE IX

Observations	Acute blood loss (upper picture)	Chronic lead poisoning (lower picture)
Red-cell count (10^6/mm^3)	2.5	2.8
Hemoglobin (gm/100 ml)	8.7	8.7
Hematocrit (percent)	26	26
Red-cell indices		
MCV [mean corpuscular volume (μ^3)]	104	93
MCHC [mean corpuscular hemoglobin concentration (gm/100 ml)]	34	33
MCH (mean corpuscular hemoglobin ($\mu\mu$g)]	35	31
Reticulocytes (percent)	9	8
Stippled cells (percent)	0	2.8
White-cell count (10^3/mm^3)		6.6
Icterus index (units)	5	5

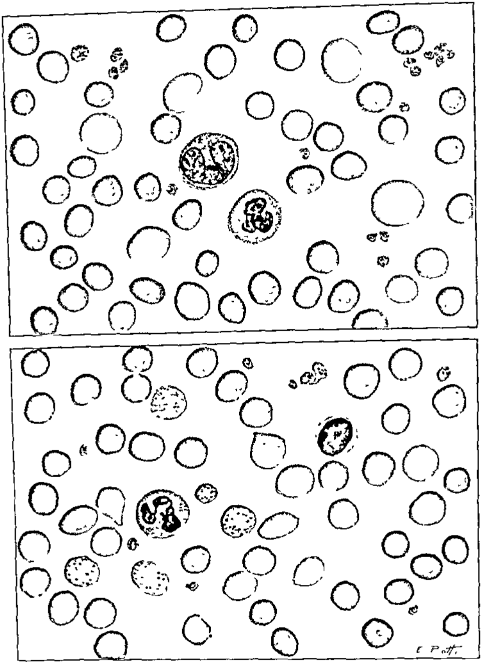


PLATE IX. ACUTE BLOOD LOSS. CHRONIC LEAD POISONING

15. PLATE IX. ACUTE BLOOD LOSS; CHRONIC LEAD POISONING

1. *UPPER PICTURE: ACUTE BLOOD LOSS* (physiologic response of bone marrow).

(*a*) DESCRIPTION. The red cells show slightly more than normal variation in size The average size of the new young polychromatophilic cells (*7*) is slightly increased and there are some cells present that are slightly smaller than the normal cells (*4*); there is practically no variation in shape. The hemoglobin content of the cells is about normal One target cell is present (*9*) The white cells include a typical neutrophil (*1*) and monocyte (*3*) The platelets (*10*) are about normal in number, but some are large

(*b*) INTERPRETATION. This is the blood picture in a young woman, *25* years of age, ten days after the onset of acute blood loss from menorrhagia. There was no evidence of chronic blood loss The polychromatophilic cells (reticulocytes 9 percent, Plate IX and Table 10) represent the immature red cells which appeared in the peripheral blood as a normal physiologic response to the acute *blood loss in a patient with iron deficiency At the* time when these young red cells are present in increased numbers, the mean corpuscular volume is increased (104 μ^3) and the mean diameter of the cells is also greater than normal

The variation in size might be confused with that observed in moderate hypochromic, microcytic anemia (Plate IV, upper picture) However, the red-cell indices in this patient show slight macrocytosis and normochromic red cells Also, the cells of this blood film, when compared with those of a normal blood, are seen to be well filled with hemoglobin Hemolytic anemia must be considered because of the presence of polychromatophilic cells, the slight macrocytosis, and the variation in size The normal icterus index is evidence against increased destruction of red cells, but does not exclude it completely The final diagnosis depends upon the recovery from the anemia with or without administration of iron therapy

2 *LOWER PICTURE· CHRONIC LEAD POISONING*

(*a*) DESCRIPTION The red cells in this blood film appear normocytic with slight variation in size but very little variation in shape. The hemoglobin concentration of the cells is normochromic. The striking abnormality here is the presence of a large number of stippled cells (*8*) and polychromatophilic cells (*7*) Stippling may occur in either the adult red cell or the younger form (polychromatophilic cell) The stippling is observed in a film stained with Wright's stain alone and does not require staining with brilliant cresyl blue Stippling should not be confused with the reticulum of young red cells (see Plate I), which does require brilliant cresyl blue for its demonstration The stippling varies in degree from coarse granules to fine punctate material

The white cells include a normal neutrophil (*1*) and lymphocyte (*2*) The platelets (*10*) appear normal

(*b*) INTERPRETATION Although the presence of stippled cells alone does not necessarily indicate chronic lead poisoning, the occurrence of stippled cells and polychromatophilic cells, associated with normal or *slightly hypochromic red cells, does suggest lead poisoning* According to the data in Table 10, there is a moderate, normocytic anemia with increased reticulocytes (8 percent) and a normal icterus index Accordingly, the large number of stippled cells, which represent 2 8 percent of the red cells, serves as a clue to distinguish this case from that of acute blood loss (upper picture) or hemolytic anemia Stippled cells, however, are also characteristic of Cooley's trait and of many other anemias, but usually are fewer in number and are associated with other changes in the red cells. The diagnosis of chronic lead poisoning may be confirmed by the history of exposure to lead and by demonstrating an abnormal excretion of lead and coproporphyrin in the urine (*Syllabus*, Unit 18, p 292). Since the type of porphyrin excreted in lead poisoning is abnormal, it is possible that the stippling of the red cells is an expression of a disturbance in metabolism or retardation of the formation of hemoglobin *[180]* The anemia does not respond to the usual antianemia therapy, but it does respond to regression of the lead poisoning

16. PLATE X. MYELOGENOUS LEUKEMIA

1. *DESCRIPTION OF BOTH PICTURES* The pictures represent blood films from two patients with chronic myelogenous leukemia

(*a*) White Cells By a study of these plates, practically all the typical cells in the development of the granulocytic series can be identified In the upper picture there are two neutrophils (*1*) and two young neutrophils or band forms (*3*) One of these band forms is much younger than the other and by some might be classed as a metamyelocyte The nucleus, however, has two lobes connected by a band, like a dumbbell The character of the nucleus is mature, with clumped chromatin A typical eosinophil (*2*) is shown with large discrete red-orange granules Three basophilic cells (basophils) are present — a young basophil (*5*), an abnormal form (*6*), and a basophilic myelocyte (*12*) The basophilic granules in the myelocyte B (*12*) should be contrasted with the neutrophilic granules of myelocyte B (*10*) The dark-blue basophilic granules are definitely larger than those of the neutrophilic myelocyte (*10*), but are usually smaller than the basophilic granules in the more mature basophils (*5* and *6*) Eosinophilic myelocytes (*11*) are striking because of the large red-orange granules which cover the round nucleus The granules in one of the eosinophilic myelocytes do not have their full color, although they are large (In other patients with myelogenous leukemia, the eosinophilic myelocytes frequently contain granules that are smaller than those shown in Plate X Occasionally, both eosinophilic and basophilic granules occur in the same cell) There is considerable contrast between the eosinophilic myelocyte B (*11*) and the more mature forms — the eosinophilic myelocyte C (*9*), young eosinophil (*4*), and adult eosinophil (2)

In the lower picture all stages of the neutrophilic series of granulocytes are shown The typical myeloblast (*14*) is shown with a fine granular nucleus containing a nucleolus, and surrounded by a rim of deeply basophilic cytoplasm, without granules A similar cell (*13*) with a typical " blast " nucleus and basophilic cytoplasm but containing nonspecific azurophilic granules, is called a myelocyte A, or early myelocyte By many observers, this could be considered a blast because of the nucleolus The granules in the cytoplasm are not differentiated into neutrophilic, basophilic, and eosinophilic types until the cell is at a more mature stage (myelocyte B) The myelocyte B of all types has already been described (*10, 11, 12*) The myelocyte C, containing neutrophilic granules (*8*) has the same type of nucleus and cytoplasm as the neutrophilic myelocytes of stage B (*10*) However, the granules, which are scattered throughout the cytoplasm, do not cover the nucleus The homogeneous nuclear structure and the light gray-blue color of the cytoplasm are the same in both the myelocyte B and myelocyte C Occasionally, the granules in the myelocyte C are absent or poorly stained, although this stage of development may be identified by comparing it with the myelocyte B of the same film The metamyelocyte (*7*) should not be confused with the myelocyte C (*8*), since the cytoplasm of the metamyelocyte has acquired the pink-lavender color of the neutrophil with a nucleus that is beginning to show slight condensation of chromatin This metamyelocyte may be compared with the band form and adult neutrophil in the same film for the color of the cytoplasm In the young neutrophil (*3*), the two lobes of the nucleus are distinct but connected by a thick band whereas in the adult form of the neutrophil the lobes of the nucleus are separated by threads of chromatin.

The young form of the monocytic series (*15*), shown in the upper picture, is often confused with the metamyelocyte (*7*) or the late myelocyte (*8*). However, the young monocyte with a round nucleus has the same lacy or reticular structure of the nucleus and often the same folded or fissured outline of the nuclear chromatin as in the lobulated nucleus of the mature monocyte (see Plate II, *10*) The differentiation of these cells may best be made by comparison with known cells of the same series in the same film The young monocyte should be compared with the adult monocyte for size, nuclear structure, color of the cytoplasm, and type of granulation The myelocyte C should be compared with the myelocyte B of the same film The nuclear structure of these cells, as shown in Plate X, is quite different Thus, the monocyte has a reticular, fissured nucleus, the metamyelocyte shows the first stages in the condensation of the chromatin that occurs as the cell matures, whereas the myelocyte C has a homogeneous nucleus Similarly, the cytoplasm of the three varieties of cells should be

. .

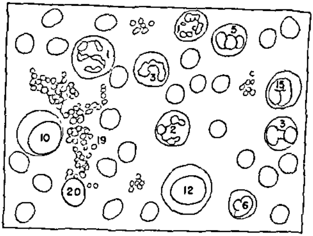
but the relative number is small since the increase is due to cells of the granulocytic series

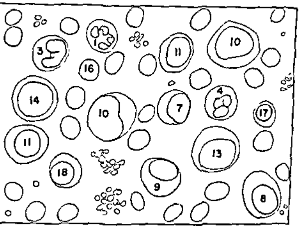
(*b*) Red Cells and Platelets. The red cells show some variation in size and intensity of staining A normoblast (*17*) and late erythroblast (*18*) are present in the lower film In both cases the platelets appear to be increased There are masses of platelets (*19*) in association with a megakaryocyte nucleus (*20*) The mega-

PLATE X MYELOGENOUS LEUKEMIA

Key

1 Neutrophil
2 Eosinophil
3 Young neutrophil (band)
4 Young eosinophil
5 Young basophil
6 Abnormal basophil
7 Neutrophilic metamyelocyte
8 Neutrophilic myelocyte C, or late myelocyte
9 Eosinophilic myelocyte C
10 Neutrophilic myelocyte B
11 Eosinophilic myelocyte B
12 Basophilic myelocyte B
13 Myelocyte A, or early myelocyte
14 Myeloblast
15 Young monocyte
16 Normal red cell
17 Normoblast
18 Late erythroblast
19 Platelets
20 Megakaryocyte nucleus





karyocyte nucleus (*20*) shows a typical dark rim surrounding masses of chromatin appearing as a wavy structure

2 *INTERPRETATION RELATED TO LEUKEMIA* There is little doubt about the diagnosis when blood films such as those shown in Plate X are seen The obvious diagnosis is myelogenous leukemia, because both films are characterized by an extreme increase in the white-cell count and immaturity of the granulocyte series of cells representing all stages The changes are an order of magnitude greater than occurs in nonleukemic conditions The abnormalities of the red cells and platelets are also consistent with the complications of leukemia — replacement of the marrow with leukemic tissue The prognosis of a given case can be estimated in part by an appreciation of the degree of abnormalities in the film

(*a*) UPPER PICTURE — CHRONIC MYELOGENOUS LEUKEMIA In the case with this blood picture, the prognosis is consistent with a chronic process and the patient may be aided considerably by treatment This prognosis is indicated by the considerable maturity of the granulocytic series The youngest cells present are the stage of myelocyte B The presence of basophilic cells in increased numbers is of interest, since basophilic myelocytes are frequently increased in untreated chronic myelogenous leukemia They may also be relatively increased after radiation therapy, although the absolute number is probably no greater than the pretreatment level [37] After prolonged radiation therapy, the cells become more and more abortive This is especially true in the basophils in chronic myelogenous leukemia Cases in which many basophilic cells have been observed throughout the disease have been called basophilic leukemia [26, 51] The red cells in this blood film seem quite normal in appearance, but the patient has a significant anemia (see Table 11) The platelets are increased and located in the vicinity of a nuclear fragment of a megakaryocyte These are frequently seen in the peripheral blood of chronic myelogenous leukemia [122, 124]

(*b*) LOWER PICTURE — ADVANCED CHRONIC MYELOGENOUS LEUKEMIA The prognosis of the patient whose blood film is represented in the lower picture is consistent with an advanced stage of chronic myelogenous leukemia This is indicated by the marked degree of im-

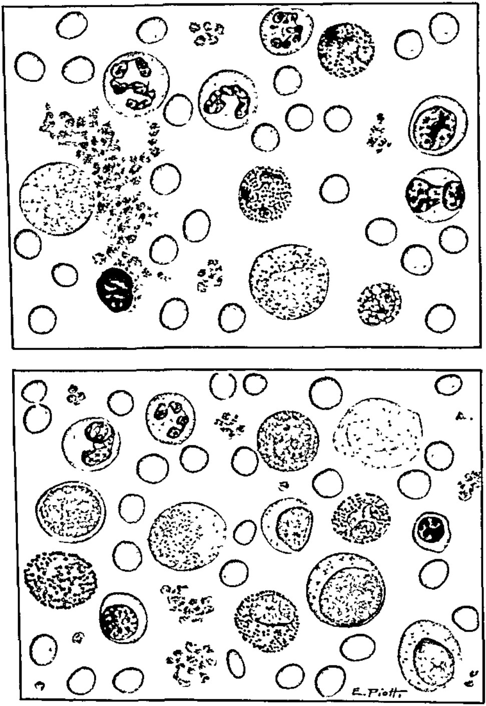


PLATE X. MYELOGENOUS LEUKEMIA

maturity of the granulocytic series, which is represented in this instance by the presence of myeloblasts, and by the presence of nucleated red cells The platelets are markedly increased A marked increase or a marked decrease in the number of platelets indicates extensive involvement of the bone marrow and is consistent with a bad prognosis

(c) ACUTE MYELOGENOUS LEUKEMIA Some cases of *leukemia show a more immature blood film than that* shown in either of these pictures When the predominating cells in the peripheral blood are myeloblasts, the leukemia is considered to be acute or the terminal phase of a chronic leukemia. The myeloblasts in such acute leukemias may be present in many abnormal forms. Some myelocytes may be present with the myeloblasts, an observation which *may aid in the identification of the* blast form as a myeloblast. Some nucleated red cells are usually present in acute leukemia The platelets may be markedly decreased in number, large, and abnormal in appearance Anemia or hemorrhage may be a major cause of death

(d) SUBLEUKEMIC OR ALEUKEMIC LEUKEMIA If the white-cell count were low, then the interpretation of these blood films would be more difficult Patients with leukopenia or normal white-cell counts, but with myelocytes or myeloblasts and often nucleated red cells in the blood, may be said to have "subleukemic" myelogenous leukemia In instances of aleukemic myelogenous leukemia, there may be no, or only a few, abnormal forms of the granulocytic series in the peripheral blood, and a low or normal white-cell count, but there may be nucleated red cells and thrombocytopenia In these instances of subleukemic or aleukemic leukemia, the diagnosis may be confirmed by bone-marrow puncture or by observing the development of the disease, which may become manifest as leukemia as it advances

3 INTERPRETATION RELATED TO MYELOID REACTION IN OTHER CONDITIONS

(a) AGNOGENIC MYELOID METAPLASIA OF THE SPLEEN [101] (CHRONIC NONLEUKEMIC MYELOSIS [25, 92], LEUKO-ERYTHROBLASTIC ANEMIA WITH MYELOSCLEROSIS [178]) *These terms are most frequently used,* although in a recent review of the literature Block and Jacobson [15] have mentioned some 25 other designations for this syndrome In agnogenic myeloid metaplasia, *active blood formation takes place in the spleen,* liver or other extramedullary sites This condition is most easily confused with myelogenous leukemia and the importance of differentiating these two diseases has been pointed out by Jackson, Parker, and Lemon [101], by Hickling [92] and by Block and Jacobson [15] Agnogenic myeloid metaplasia may be associated with exposure to industrial solvents such as benzol, and may be preceded by polycythemia For example, of 15 patients with erythremia reported by Minot and Buckman [123], three developed anemia and a leukemoid blood picture. The sections of the spleen of one of these have been reviewed and showed changes consistent with *agnogenic myeloid metaplasia. The description* of the blood picture in the cases described by Minot and Buckman [123] and their accompanying plate give an accurate reproduction of the changes in the red and white cells seen in the polycythemic phase of agnogenic myeloid metaplasia The clinical picture and the hematologic findings vary markedly, especially as the disease progresses. The essential physical finding is progressive and extreme enlargement of the spleen without lymphadenopathy

The blood film is characterized by marked variation *in size and especially in the shape of the red cells, with* nucleated red cells The presence of nucleated red cells, occurring when the red-cell count is $4 \times 10^6/mm^3$ or as high as 6 or $7 \times 10^6/mm^3$ in cases of polycythemia, is a finding of diagnostic importance In myelogenous leukemia, the red-cell changes early in the disease usually are not so great as in myeloid metaplasia In myeloid metaplasia, the red cells show tailed forms, microcytes, and many bizarre forms that are more characteristic of myelophthisic anemia than of any other anemia Stippled cells, Cabot ring forms, Howell-Jolly bodies, and *polychromatophilic cells are found as the disease* progresses Continuing reticulocytosis is characteristic, with occasional cases in the anemic phase showing values as high as 30 percent. A few cases have been observed in *which an overwhelming hemolytic anemia has been* present [20, 101]

The presence of immature cells of the granulocytic series occurring when the white-cell count is low or normal and the red-cell count is normal or increased is also characteristic As the disease progresses, more immature cells appear and in some cases the white-cell count may increase to $200 \times 10^3/mm^3$, making the clinical differentiation from myelogenous leukemia difficult or impossible The condition may occasionally terminate in leukemia The disease may be one of prolonged chronicity (20 years) with extreme splenomegaly and with the blood picture described above In some cases the platelets have been increased, as in myelogenous leukemia, associated with fragments of megakaryocyte *nuclei in the film Platelets* may be large and extremely bizarre In other cases, thrombocytopenic purpura may be the presenting symptom Splenectomy may be fatal, since active blood formation is taking place in the *spleen, although in some instances* patients have lived many years [37, 148] following removal of the spleen

(b) MYELOPHTHISIC ANEMIA In carcinoma arising in the breast, prostate, thyroid, stomach or kidney, the presence *of myelocytes, myeloblasts,* and nucleated red

TABLE 11 LABORATORY DATA FOR PLATES X AND XI

Observations	Myelogenous leukemia		Monocytic leukemia	
	Upper picture	Lower picture	Upper picture	Lower picture
Red-cell count (10^6/mm^3)	3.5	2.4	1.4	1.8
Hemoglobin (gm/100 ml)	9.2	7.6	5.3	6.0
Hematocrit (percent)	29.8	22.6	15.8	18.7
Red-cell indices				
MCV [mean corpuscular volumes (μ^3)]	85	95	111	104
MCHC [mean corpuscular hemoglobin concentration (gm/100 ml)]	31	34	34	32
MCH [mean corpuscular hemoglobin ($\mu\mu g$)]	26	31	37	33
Reticulocytes (percent)	2	4	1.1	1.5
Nucleated red cells (per 100 white cells)	1	5	1	2
Icterus index (units)	—	—	3	5
Platelet count (10^3/mm^3)	300	250	146	90
White cell count (10^3/mm^3)	50	94	43	76
Differential white-cell count (percent)				
Neutrophils, adult	27	15	9	10
Neutrophils, band	15	16	14	5
Eosinophils	2	3	1	
Basophils	10	2		
Metamyelocytes	2	11		1
Myelocytes C, neutrophilic	5	11		2
Myelocytes C, eosinophilic	1	4		
Myelocytes B, neutrophilic	24	19		
Myelocytes B, eosinophilic	1	4		
Myelocytes B, basophilic	5	2		
Myelocytes A	0	3		
Myeloblasts	0	7		
Lymphocytes	5	2	5	16
Monocytes, adult	3	1	40	20
Monocytes, young			27	21
Monoblasts			4	23
Histiocytes				2

ls in the peripheral blood may be the first evidence it metastasis to the bone marrow has occurred [88, , 102, 174] In carcinomatosis there may be a high ite-cell count, an increase of myelocytes, occasional ,eloblasts, and toxic granulation of the neutrophils A nilar leukemoid response of the myeloid type may be en in disseminated tuberculosis [99, 173] or when the *ne marrow is invaded by lymphoma or leukemic tis-* : The presence of nucleated red cells when the red-l count is above 4×10^6/mm^3, and of abnormal cells the granulocytic series when the white-cell count is rmal or slightly increased, should be considered as ssible signs of invasion of the bone marrow

(*c*) DISEASES OF INFANTS AND CHILDREN The bone irrow in infants and children is labile and therefore e physiologic response to blood loss infection, and her hematopoietic stimuli is markedly myelocytic iis is especially true in infants The myeloid reaction an infant was reported by Buckman [21] in which e white-cell count rose to 84.5×10^3 mm^3 with 9 percent of myelocytes and 7.5 percent of "endothelial cells" Megakaryocyte fragments were seen and there were nucleated red cells in the peripheral blood

(*d*) CHRONIC OR ACUTE INFECTIONS Severe infections with increased counts of white cells and immature cells of the granulocytic series may sometimes be confused with leukemia In such cases, the neutrophils and *precursors may show toxic granulation which is not usu-*ally seen in the uncomplicated chronic myelogenous leukemia For example, a severe streptococcus infection in a patient with sickle-cell disease was first diagnosed as leukemia before the red-cell changes with nucleated red cells were recognized as related to the underlying sickle-cell anemia [37] Leukemoid responses have been reported [107] in septicemia, and in chronic and acute infections [56, 88 173]

(*e*) ACUTE BLOOD LOSS Acute blood loss, whether external or internal, may produce a myeloid response in the peripheral blood

(*f*) ACUTE HEMOLYTIC ANEMIA A leukemoid response of the myeloid cells may appear in severe hemolytic anemia following transfusion reactions, in acquired hemolytic jaundice with antibody sensitization of red cells, and following severe burns associated with anemia and necrosis of tissues A leukemoid blood picture may follow the hemolytic anemia resulting from the use of drugs, such as sulfanilamide [93] or mercurial ointments [56], or in benzol poisoning [145]

(*g*) AGRANULOCYTOSIS. Although the white-cell count is very low in agranulocytosis, immature cells of the myeloid series, including myeloblasts, have been seen during the period of recovery [37].

17. PLATE XI. MONOCYTIC LEUKEMIA

1 *DESCRIPTION OF UPPER PICTURE.* The predominating cells in this film are large cells with gray-blue cytoplasm, finely peppered with granules that are concentrated around the periphery. The granules are usually blue-purple but are sometimes azurophilic. These cells are different stages of the monocytic series As described previously (p 20), the nucleus of the monocyte is somewhat irregular in outline, is not sharply defined as is the lymphocyte nucleus, and has a lacy, reticular chromatin structure which may have a folded or grooved appearance. As seen in this picture, this lobulation is apparent in the adult monocyte (*6*) and in the young monocyte (*7*) and even in the blast (*8*) The nucleus of the mature monocyte (*6*) is indented and the lobes are more striking than in the cells classed as young forms (*7*), which have a round nucleus This may also be observed in Plate II, in which the monocytes have a typical horseshoe shape. These characteristics should permit differentiation of the monocytic series from the pink-lavender cytoplasm and clumped chromatin nucleus of the neutrophil (*1*) and band form (*2*) The monocyte is nearly always much larger than the neutrophil In infectious states, abnormally large band forms may be confused with the monocyte In such instances, the characteristics of the known cells must be compared with those of the unknown The small lymphocyte (*3*) with clear light-blue cytoplasm and sharply defined nucleus with condensed chromatin would not be confused with the monocytic series as shown in this film The red cells are quite uniform in size and shape, but are slightly macrocytic The platelets are slightly decreased

2 *DESCRIPTION OF LOWER PICTURE* In this film the predominating cells are young monocytes (*7*) and blasts (*8*) These are considered monoblasts because they have the same type of folded nucleus as is present in the young and adult monocytes The three monoblasts (*8a*) with nucleoli represent the youngest cells The nucleoli are sharply defined areas in the nucleus that take a lighter stain. The nuclear chromatin is slightly more reticular in these blasts than in the myeloblast (Plate X) or the lymphoblast (Plate XII) Azurophilic granules may be present in the monoblast and may represent a stage of maturation comparable to the myelocyte A stage of Fig 4. Azurophilic rods or Auer bodies are present in the cytoplasm of some of these monoblasts (*8b*). It should not be difficult to distinguish the myelocyte with its homogeneous nucleus, sometimes covered with granules (*4*), from the monocyte with its loose reticular nucleus The histiocyte (*5*) in the lower right-hand corner should be observed with care, since this cell is often incorrectly classed as a monocyte The histiocyte is characterized by the irregular contour of the cell, the spongy, vacuolated cytoplasm which may or may not show active phagocytosis, and the honeycomb structure of the nucleus The red cells show moderate variation in size The platelets are definitely reduced, as occurs in most acute leukemias

3 *INTERPRETATIONS*

(*a*) RÉSUMÉ OF CASES These blood films are from two patients with monocytic leukemia (A47-30 and A45-310 *) The patient whose blood film is shown in the *upper picture* was a 73-year-old woman who entered the hospital because of anemia (red-cell count, 1.4×10^6/mm³; hemoglobin, 5 3 gm/100 ml) She had noted progressive weakness and exertional dyspnea for approximately one year Her diet had been markedly restricted in variety and amount. There were two previous admissions, seven and twelve years before, with diagnoses of psychoneurosis, malnutrition, and vitamin deficiency Aspiration of the bone marrow on her last admission showed hyperactivity of granulocytic, monocytic, and erythrocytic series with extremely young red cells She was first considered to have a nutritional macrocytic anemia and was given liver extract, but her anemia did not respond to therapy Her white-cell count on admission was 7.1×10^3 mm³ with 34 percent of monocytes The white-cell count increased steadily while under observation to 300×10^3 mm³ and the proportion of monocytes increased to 92 percent Throughout the period of observation the characteristic cells were the large monocytes with gray-blue cytoplasm containing fine scattered blue-purple granules and typical lobulated nuclei with the loose lacy structure Young monocytes and monoblasts were present, but the mature

* Mallory Institute of Pathology, Boston City Hospital

forms predominated The duration of the disease after the diagnosis of leukemia became manifest was only one month Although her presenting symptoms at this admission were those of anemia, presumably related to the leukemia, it is impossible to judge how long the leukemic process had been active

The blood film shown in the *lower picture* was from a 41-year-old man with severe anemia, thrombocytopenia, and high white-cell count The clinical manifestations at this time were typical of an acute leukemia with a sudden onset 5 days before admission, symptoms of a mild upper-respiratory infection and slight sore throat, headache, and pain in the arms and legs and back The patient had nosebleeds, petechiae, gastro-intestinal hemorrhage, and bleeding from a rectal fistula An ischiorectal abscess had been operated upon five months previously, but it had not healed properly; no data on the blood film at that time are available The patient had a rapid downhill course, death occurring after 20 days in the hospital. In contrast to the other case, the white blood cells were chiefly monoblasts and young monocytes

(*b*) Prognosis in Monocytic Leukemia It is difficult to distinguish between acute monocytic leukemia and a terminal phase of a chronic monocytic leukemia Patients have been observed who have shown an increased count of monocytes, largely adult forms, over a period of many months This has been followed subsequently by clinical manifestations of leukemia and the appearance of increased numbers of young monocytes and monoblasts in the peripheral blood during a terminal "leukemic" period of two months [11] Chronic monocytic leukemia occurs, although definite diagnosis often is not established until the patient has an acute fulminating infection or hemorrhagic manifestations associated with an acute phase of the monocytic leukemia [71] When the peripheral blood contains monoblasts, the prognosis is poor However patients have been observed with mature monocytes in their peripheral blood associated with the symptoms and signs of an acute type of leukemia with gum lesions and hemorrhagic phenomena The duration of life is influenced in part by the control of the infection with drugs and antibiotics

(*c*) White-Cell Count in Monocytic Leukemia The white-cell count varies widely from normal values up to several hundred thousand per cubic millimeter The predominating cell is the monocyte A given case may show mature forms as the predominating cell, monoblasts as the characteristic form or in most instances different stages in maturation of the monocyte As the disease progresses the type of monocyte may become more and more immature Young neutrophils and myelocytes may also be seen, but rarely in numbers great enough to cause confusion Myelocytes may be present in any leukemia or anemia

(*d*) Auer Bodies The Auer bodies shown in some of these cells (*8b*) are characteristically seen in acute leukemias [3] Although they were originally described as occurring in lymphocytes [4], with a better differentiation of the blood cells it is now recognized that they occur in myeloblasts [152], in monoblasts in many cases of monocytic leukemia, in histiocytes or reticulum cells, and in plasma cells [37, 71, 78, 111] According to Leitner [111], these Auer bodies are crystals of abnormal protein

(*e*) Anemia A normocytic anemia (rarely macrocytic as in these cases) of moderate to severe degree is usually present by the time a diagnosis of monocytic leukemia can be made Nucleated red cells are often present as one of the characteristics of a myelophthisic anemia

(*f*) Platelets The platelet count is usually decreased This may be manifest, occasionally as a presenting complaint, by hemorrhagic phenomena, as was observed in the patient whose blood film is shown in the lower picture

4 *MONOCYTIC LEUKEMIA DIFFERENTIATED FROM OTHER LEUKEMIAS* The separation of monocytic leukemia from other leukemias was first described by Reschad and Schilling-Torgau in 1913 [150] The hypothesis of Ehrlich [60] that the monocyte was a transition form between the myelocyte and the neutrophil impeded progress in the understanding of this cell Naegeli [131] and Evans [64] concluded that the monocyte was an independent cell type of myeloid origin Still further confusion has resulted because the monocyte has not been differentiated by many observers from the histiocyte or reticulum cell The theories of origin of the monocyte have been confusing Forkner [71], for example, cites 16 theories on the origin of the monocyte

Clough [30] reported 22 cases of monocytic leukemia from the literature and one of his own, but did not differentiate the monocyte from the histiocyte Forkner [71] differentiated acute monocytic leukemia from acute lymphocytic and acute myelogenous leukemia Other reviews of monocytic leukemia are given by Osgood [135] and Evans [65]

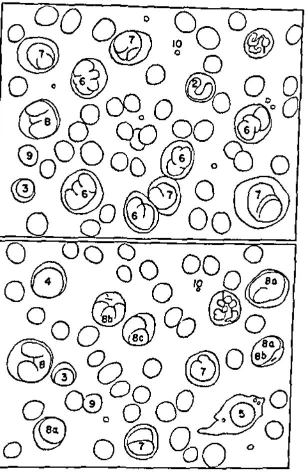
In the majority of instances, monocytic leukemia need not be confused with either the myelogenous leukemia or the histiocytic leukemia if the type of cell is studied Although small numbers of myelocytes may be present in a monocytic leukemia, and occasionally there appears to be a "shower" of monocytes in a myelogenous leukemia, these two leukemias are readily distinguished It is necessary to evaluate the blood by making more than one observation For example, Hall and

PLATE XI MONOCYTIC LEUKEMIA

Key·

1. Neutrophil
2. Young neutrophil (band)
3. Small lymphocyte
4. Neutrophilic myelocyte B
5. Histiocyte
6. Monocyte, adult
7. Monocyte, young
8. Monoblast

8a Monoblast showing definite nucleoli
8b Monoblasts with Auer bodies
8c Monoblasts with azurophilic granulation
9 Normal red cells
10 Platelets



Watkins [83] report a case changing from myelogenous to monocytic leukemia, probably indicating an early myeloid response in a patient with underlying monocytic leukemia

Watkins and Hall [179] have shown that the Schilling type of monocytic leukemia can be distinguished from the Naegeli form of monocytic leukemia by the morphologic characteristics of the predominant cell and its progenitors and from the histopathologic findings in the hematopoietic tissues The Schilling type of monocytic leukemia appears to be a separate entity and is called by some leukemic reticulo-endotheliosis (or histiocytic leukemia) A series of leukemia cases have been studied by Belding, Daland, and Parker [11] in which differentiation of histiocytic leukemia from the monocytic leukemia has been possible by hematologic pathologic, and morphologic studies

5 *MONOCYTIC RESPONSE — MONOCYTOSIS* The evaluation of the literature in regard to monocytic responses must also be carefully considered with respect to the type of cell described The response of histiocytes and clasmatocytes has been termed a "mononuclear" reaction throughout the literature, but is discussed separately (Sec 18), since these are not cells of the monocytic series

Monocytes are often increased during the recovery phase of agranulocytosis They are also increased following acute infection and in pneumonia during the period of resolution of the pulmonary process, in the acute phase of rheumatic fever [37], in some instances of acute inflammation [72], and, in many patients, in the active phase of tuberculosis *[13, 73, 118]* Also, the increase in the number of monocytes was found to be of diagnostic importance in selecting, before clinical symptoms developed, the patients who were getting tetrachlorethane poisoning [126] In conditions associated with monocytosis, the course of the blood findings and the clinical manifestations over a period of time usually serve to differentiate them from monocytic leukemia Occasionally, the differentiation is obtained only at autopsy, in which the presence or absence of infiltration of the organs by the monocytic leukemia is the criterion for the diagnosis or exclusion of the diagnosis of leukemia

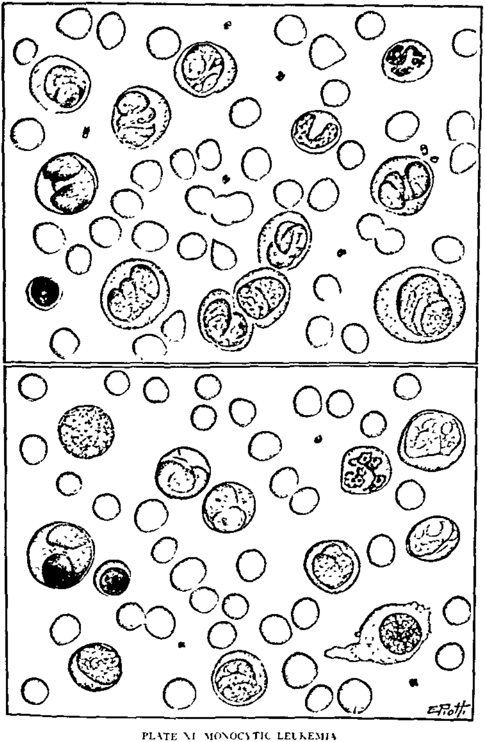


PLATE XI MONOCYTIC LEUKEMIA

18. HISTIOCYTIC LEUKEMIA AND HISTIOCYTES IN OTHER CONDITIONS (Fig. 8)

1. *HISTIOCYTIC LEUKEMIA* (Fig 8, *6*, *7*, and *8*). It is believed that histiocytic leukemia can be differentiated from monocytic leukemia clinically, hematologically, and pathologically [11]. Histiocytic leukemia has been called the Schilling type of monocytic leukemia by Watkins and Hall [179] Dameshek [41] has brought together much of the early literature on histiocytic leukemia and reported additional cases

Although histiocytic leukemia may be manifest in some patients, in many there is marked leukopenia. In such cases, only a few large abnormal cells or blasts may be encountered in the peripheral blood, so diagnosis is difficult. The histiocytes may be amoeboid, phagocytic, or blast forms, as described on p *21* The number of monocytes is less than normal and myelocytes may be rarely seen These patients should be observed repeatedly, since more abnormal cells may appear with the progress of the disease and bone-marrow aspirations may be of diagnostic value Most patients with histiocytic leukemia show a marked normocytic anemia with the presence of occasional nucleated red cells. The platelets are definitely decreased

2 *HISTIOCYTES IN RETICULUM-CELL SARCOMA* (Fig 8, *3*) Amoeboid histiocytes or histiocytes with basophilic cytoplasm have been seen occasionally in the peripheral blood during the course of reticulum-cell sarcoma There may be leukopenia, normal white-cell count, or an elevated white-cell count due to histiocytes Bone-marrow biopsy may be of value in instances of low white-cell count or when histiocytes appear in the peripheral blood Several cases of "reticulosis" are presented by Ross [153] with a review of the literature Other references of value are given by Leitner [111]

3 *HISTIOCYTES IN HODGKIN'S SARCOMA* (Fig 8, *5*) The relation of the "monocytosis" to Hodgkin's disease is confusing in the literature because of the debate concerning the origin of the monocyte and the histiocyte and because of the use of such terms as "reticulo-endotheliosis" and "aleukemic reticulosis" In a patient (PH19588) reported by Merrill [120], a leukemic picture was present during the last hospital admission, the white-cell count varying from 4 0 to 2 0 × 10³/mm³ The abnormal cells, which varied from 2 to 36 percent, were large irregular forms, with deep-blue cytoplasm and nuclei of homogeneous chromatin with nucleoli These were considered to be histiocytes Other cases have been observed [37] with histiocytes of various types appearing repeatedly in the film of peripheral blood In the review by Dameshek [42], a relation between the aleukemic reticulosis and Hodgkin's disease is suggested. Marchal and Bargeton [115] claim that Hodgkin's sarcoma may show a terminal "monocytosis", these "monocytes" presumably are histiocytes.

4 *HISTIOCYTES IN ANEMIA* (Fig 8, *4*) Ehrlich [60] probably was the first to describe "mononuclear erythrophagocytosis" Abt [2] observed erythrophagocytosis in a newborn infant with anemia. Histiocytes have been observed many times in the peripheral blood in pernicious anemia Rowley [155] has published a case of anemia characterized by marked phagocytic activity in the peripheral blood by the histiocytes Histiocytes showing active phagocytosis have frequently been seen in hemolytic anemia

5. *HISTIOCYTES IN BACTERIAL INFECTIONS* (Fig 8, *1* and *2*) The most striking occurrence of the phagocytic histiocyte in the blood stream has been seen in subacute bacterial endocarditis [37, 143] A patient with typhoid fever showed many amoeboid and phagocytic histiocytes in the peripheral blood (Fig 8, *2*) [37] In overwhelming sepsis a terminal shower of histiocytes has been observed [37]. Thirty percent of histiocytes (abnormal "monocytes") were seen in a case of meningitis (A36-601 *), and *52* percent of histiocytes ("amoeboid forms of abnormal cells") were found in a terminal state in a patient with pneumonia Another patient with peritonitis showed 18 percent of histiocytes just before death (A44-105 *) There was no evidence of leukemia in these patients

6 *HISTIOCYTES IN VIRUS INFECTIONS* The young type of "abnormal lymphocyte" seen in infectious mononucleosis, infectious hepatitis, and chicken pox resemble some of the cells seen in histiocytic leukemia and the terminal phase of Hodgkin's sarcoma It is possible that this type of cell is produced from the cellular reticulum of the lymph node "Aschoff indicated that the germinal centers of the lymph nodules are centers for proliferation of reticulum cells (histiocytes) and for elaboration of antibodies," as quoted by Foot [70] in his report on endothelial phagocytes. Bunting [22] in one of his early papers spoke of the hyperplasia of reticulum cells of the lymph nodes that took place when there was a lymphocytic reaction as a result of antibody production Lymphocytic histiocytes have been described in Sec 6 (6d)

7 *HISTIOCYTES IN PARASITIC DISEASES AND RICKETTSIAL DISEASES* In malaria, histiocytes show active phagocytosis of pigment and products

* Mallory Institute of Pathology

of red-cell destruction in man [156] and in monkey [169] Foot [70] has shown the importance of histiocytes in kala azar and in amebiasis Histiocytes also play an active part in typhus and in Rocky Mountain spotted fever.

8. *HISTIOCYTES IN ALLERGIC REACTIONS.* Some of the young abnormal "lymphocytic cells" seen in serum sickness are irregular cells with basophilic cytoplasm which may be lymphocytes but, in some instances, probably are histiocytes.

9 *HISTIOCYTES IN THE STORAGE DISEASES* Modified histiocytes are characteristic of Niemann-Pick disease, Gaucher's disease, Hand-Schuller-Christian disease, and hemochromatosis Although these cells are of diagnostic value in aspiration of spleen and bone marrow, they are only rarely seen in the peripheral blood [170] Lipoid histiocytosis has been described by Baty [8] in a case of Niemann-Pick disease in which a leukocytosis of from 12 0 to 35 0 $\times$ 10^3/mm^3 occurred, with 27 percent of the white cells containing large vacuoles of varying size scattered throughout the abundant pale-blue cytoplasm The nucleus was somewhat indented and relatively dense These cells were oxydase negative and in supravital stain showed the characteristics of clasmatocytes Blackfan and Diamond [14] described such cells as monocytes, while Bloom [16] described them as vacuolated monocytes and vacuolated histiocytes.

19. PLATE XII. LYMPHOCYTIC LEUKEMIA

1 *UPPER PICTURE: CHRONIC LYMPHOCYTIC LEUKEMIA.*

(*a*) Description The predominating cell in this film is the mature lymphocyte with its clear-blue cytoplasm The nucleus of the lymphocyte (*3*) is rather sharply defined and contains densely clumped chromatin, whereas the nucleus in the monocyte (*2*) is irregular, sometimes horseshoe-shaped, and has a delicate lacy structure or fine network

The mature lymphocyte is divided into two types according to size The small lymphocyte (*3*) has a nucleus about the size of a red cell and a relatively small amount of cytoplasm The large lymphocyte (*4*) has a nucleus larger than the red cell and usually has abundant cytoplasm The structure of the nucleus is similar to that of the small lymphocyte, but often is not so densely clumped The cytoplasm is a clear blue, the lightest blue of any of the blood cells, and occasionally contains a few scattered red-purple granules, and rarely some blue granules

Broken cells (*7*) are common in films of leukemic blood and are not included in the differential count of white cells because the cell type cannot usually be identified The red cells show slightly more than normal variation in size The number of platelets is slightly decreased

(*b*) Interpretation This picture is characteristic of the blood film seen in chronic lymphocytic leukemia Here the predominating cell is the small lymphocyte (*3*) (see p 15) Sometimes the nuclear chromatin is more densely clumped than normal, giving the appearance of plasma cells Such cells can usually be differentiated from plasma cells by the fact that the lymphocyte cytoplasm is a clear light blue compared to the green-blue of the plasma cell (see Plate XIII) Occasionally vacuoles or fenestrations of the nucleus will simulate nucleoli, but true nucleoli are usually seen in young forms with deep basophilic cytoplasm The nucleus is usually round, although certain cases of leukemia have been observed in which the nuclei have deep indentations [37]

The degree of anemia varies from none to severe myelophthisic forms with variable degrees of thrombocytopenia (*Syllabus*, Unit 15)

Chronic lymphocytic leukemia may be discovered by accident and the patient may live many years Accordingly, the identification of mature lymphocytes by careful study of the blood film is an aid in establishing the prognosis of the patient

2 *LOWER PICTURE· ACUTE LYMPHOCYTIC LEUKEMIA*

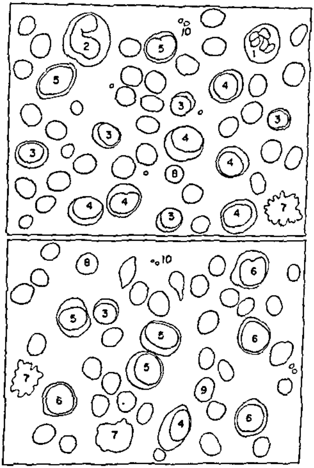
(*a*) Description The cells in this film are more immature than those shown in the upper picture The predominating cell types are the young lymphocyte (*5*) and the lymphoblast (*6*) The nucleus of the young lymphocyte does not stain so intensely as the nucleus in the small or large lymphocytes, and the chromatin is not so densely packed The nucleus is large and occupies most of the cell, leaving only a small rim of deep-blue cytoplasm The nucleus of the lymphoblast has a red-purple, finely granular chromatin structure and stains less intensely than any of the more mature forms Three of the lymphoblasts in this film have nucleoli The cytoplasm of the lymphoblast is not abundant and stains a deep blue similar to that of the young lymphocyte The lymphoblast (*6*) may be contrasted with the small (*3*) and large lymphocytes (*4*) that are present in the film Broken cells (*7*) or "smudges" are seen in increased numbers in acute leukemias and are noted but not included in the differential count of white cells

PLATE XII LYMPHOCYTIC LEUKEMIA

Upper picture Chronic lymphocytic leukemia.
Lower picture: Acute lymphocytic leukemia.

Key:

1 Neutrophil
2 Monocyte
3. Small lymphocyte
4 Large lymphocyte
5 Young lymphocyte
6 Lymphoblast
7 Broken cell or "smudge"
8 Normal red cell
9. Polychromatophilic red cell
10 Platelets



The red cells show greater variation in size and shape in the lower picture than in the upper picture, and there *is a marked decrease in the number of platelets, a fre*quent finding in acute leukemia

(*b*) INTERPRETATION This picture may be compared with the upper picture showing the chronic form of the disease This might be either an acute leukemia or the terminal stage of a chronic form The presence of lymphoblasts, changes in the red cells associated with the anemia, and thrombocytopenia, as shown in this film, are diagnostic points that give a serious prognosis for *the patient This patient lived only 3 weeks after this* initial examination of his blood was made

Anemia in these leukemias may be the result of acute or chronic blood loss because of the thrombocytopenia, or it may be a myelophthisic anemia showing nucleated red cells and myelocytes resulting from infiltration of the bone marrow

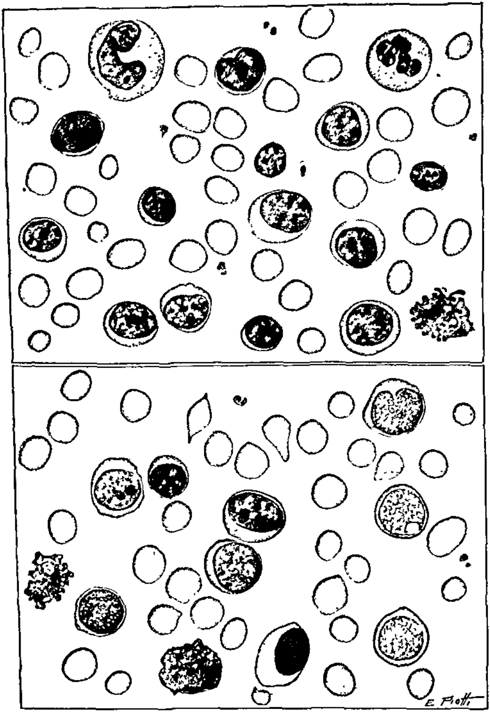
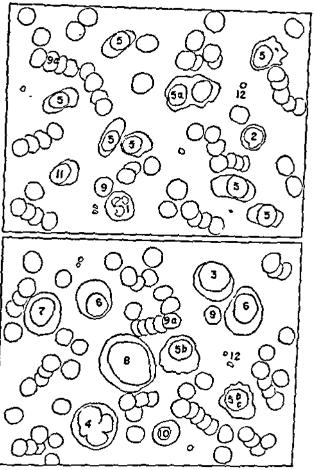


PLATE XII LYMPHOCYTIC LEUKEMIA

PLATE XIII. PLASMA-CELL LEUKEMIA

Key·

1 Neutrophil
2 Small lymphocyte
3 Large lymphocyte
4 Monocyte
5 Mature plasma cell
5a Plasma cell with two nuclei
5b Plasma cell showing irregular periphery and purple color to cytoplasm
5c Plasma cell with Russell bodies
6 Young plasma cell
7. Plasmablast
8. Stem cell
9. Normal red cell
9a Red cell in rouleau
10 Normoblast
11 Late erythroblast
12. Platelets



20. PLATE XIII. PLASMA-CELL LEUKEMIA

1 *DESCRIPTION OF UPPER PICTURE* The predominating cells in this blood film are the mature plasma cells [121] which are characterized by an elongated or oval shape with an eccentric nucleus (*5*) and, in some, by a perinuclear clear area The cytoplasm is a *characteristic gray-green-blue with a foamy or spongy* structure, sometimes containing vacuoles, and showing ragged edges This cytoplasm *is quite different from the* clear-blue cytoplasm of the lymphocyte (*2*). The mature plasma cell has a characteristic nucleus with wedges of chromatin that are distinctly separated, in contrast to the more compact nuclear structure of the lymphocyte The cell with the double nucleus is a plasma cell in division The presence of dividing cells suggests the possibility of a neoplastic disease involving the plasma cell, such as plasmacytoma (myeloma) or plasma-cell leukemia *The plasma cell is easily confused with the erythroblast* (*11*), which may have a similar nucleus but has ... vacu-
ed
e and
shape However they appear in groups or in moderate rouleaux (*9a*), which are associated with hyperglobulinemia in many but not all cases The observation of rouleaux in a thin film is indicative of increased concentrations of fibrinogen or serum globulins (*Syllabus*, Unit 12, p. 125, and Unit 13, p 137).

The platelets are normal in morphology, but appear slightly decreased in number.

2 *DESCRIPTION OF LOWER PICTURE* The types of plasma cells in this picture are more varied than in the upper picture Since many stages of plasma cells are represented, these cells are more difficult to classify Two mature forms are shown (*5*) with characteristic eccentric nuclei, oval shape, irregular outline, and a purple (rather than green-blue) reaction of the cytoplasm (*5b* and *5c*) The purple color of these cells appears to arise from a mixture of color resulting from acidophilic material and basophilic material In one of these cells (*5c*), acidophilic material appears as globules called Russell bodies [121, 142]

The young plasma cells (*6*) have a gray-green-blue cytoplasm with some vacuolated areas but *the nuclear* structure is finer than that of the mature cells These

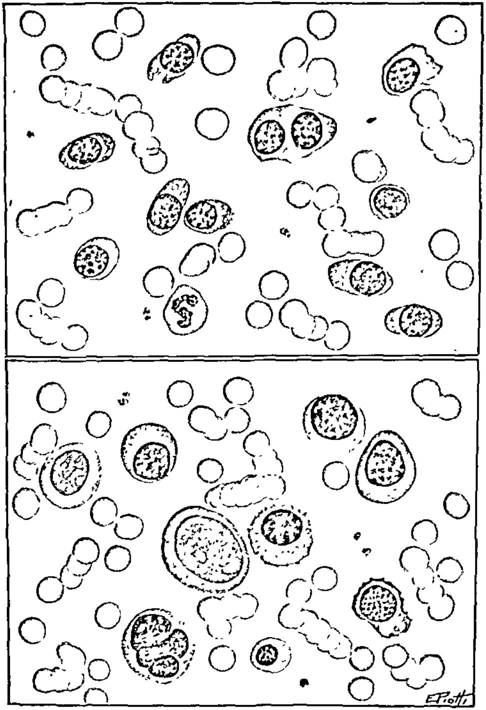


PLATE XIII PLASMA CELL LEUCEMIA

TABLE 12 LABORATORY DATA FOR PLATES XII, XIII, AND XIV

Observations	Lymphocytic leukemia		Plasma-cell leukemia		Infectious mononucleosis	
	Upper picture	Lower picture	Upper picture	Lower picture	Upper picture	Lower picture
Red cell count ($10^6/mm^3$)	3 8	2 1	2 3	3 7	4 1	5 0
Hemoglobin (gm/100 ml)	10 6	6 5	8 7	10 1	12 3	13 6
Hematocrit (percent)	36 4	19.2	25 2	33 1	39 1	40 6
Red-cell indices						
MCV [mean corpuscular volume (μ^3)]	96	92	108	89	96	81
MCHC [mean corpuscular hemoglobin concentration (gm/100 ml)]	29	35	34	31	32	33
MCH [mean corpuscular hemoglobin ($\mu\mu g$)]	28	32	37	27	30	27
Reticulocytes (percent)	0 8	—	—	1 5	—	—
Icterus index (units)	4	—	5	4	4	10
Heterophile antibody (dilution showing agglutination)	—	—	—	—	1/256	1/128
White-cell count ($10^3/mm^3$)	50 1	11 1	40 0	24 6	22 1	9 5
Differential white-cell count (percent)						
Neutrophils, adult	5	5	6	26	27	7
Neutrophils, band			21	15	9	8
Eosinophils				1		1
Basophils					1	
Myelocytes		3		3		
Lymphocytes, small	83	12	1	5	4	32
Lymphocytes, large	10	5		5	23	10
Lymphocytes, young		10		2	7	18
Lymphocytes, atypical					18	14
Lymphoblasts		65				2
Monocytes, adult	2		1	3	8	6
Monocytes, young					3	
Plasma cells, adult			32	20		2
Plasma cells, young			39	15		
Plasmablasts				5		

cells are exceedingly difficult to distinguish from the large lymphocyte (*3*), in which the cytoplasm is a clear blue The characteristic gray-green-blue or muddy blue of the immature plasmacyte aids in its identification Also, these cells are usually seen in association with some mature forms

There are two blast forms present; one is the youngest form of the plasmacytic series (*7*) and has the characteristic blue cytoplasm and vacuoles The other blast (*8*) may be considered an unidentified blast form or a stem cell The stem cell is usually much larger than the other blasts and has basophilic cytoplasm staining a much deeper blue than that of blast forms The nucleus is finely granular stains less intensely than the cytoplasm, and contains several nucleoli which are large and distinct Stem cells may be seen in any leukemic blood or severe infection that demands young cells from the hematopoietic tissues Sometimes a leukemia, characterized by young cells of this type, is called a stem-cell leukemia

This film also shows a normal monocyte (*4*) and a normoblast (*10*) The red cells show the rouleau formation that is characteristic of the diseases with high globulins

3 *INTERPRETATION OF BOTH PICTURES*

(*a*) PERIPHERAL BLOOD These pictures represent two cases of plasma-cell leukemia, which is a rare condition [129, 139] Diagnosis is not difficult when the cells are typical and mature, as in the upper picture The problem is much greater in the lower picture, where many stages of plasma-cell development are seen By carefully studying these cells, the same characteristic cytoplasm (gray-green-blue, vacuolated, or spongy) can be seen Plasma-cell leukemia is considered as the leukemic phase of plasmocytoma (multiple myeloma) [100] In the blood of both patients shown in Plate XIII there was a myelophthisic anemia

(*b*) BONE-MARROW STUDIES IN PLASMOCYTOMA A study of bone-marrow aspirations in multiple myeloma may give varied pictures in different cases In some instances, the mature plasma cell, such as is seen in the upper picture, predominates, while in others the young plasma cell or the plasmablast may predominate These young forms of plasma cells have the same characteristics as, and apparently are identical to, the so-called myeloma cell [9 10, 50 127] In some cases, the bone marrow has the variety of cells shown in the lower picture of plasma-cell leukemia

(*c*) PLASMA CELLS IN OTHER CONDITIONS Cells of the plasmacytic series may appear in the bone marrow and peripheral blood in instances of hyperplasia of the hematopoietic system and in many infections such as

measles, infectious mononucleosis, chicken pox [94], overwhelming sepsis, and serum sickness [105], and in the recovery phase of agranulocytosis [35, 111]

The Turk irritation form, reported by many observers in infectious diseases, is probably a cell of the plasmacytic series

(*d*) HISTOCHEMISTRY. The periodic acid Schiff method of McManus and Hotchkiss has been used, together with other techniques, to investigate the cytochemistry of plasma cells [142] Evidence is presented to show that the cytoplasm of human plasma cells contains mucoprotein [142], which is a polysaccharide-containing globulin If the function of the plasma cell is to produce mucoproteins, then the formation of Russell bodies may represent a disorder due to overstimulation or overproduction, The presence of mucoprotein in the cytoplasm and Russell bodies may account for their similarity in staining, as shown by the acidophilic cytoplasm and the Russell bodies in cells *5b* and *5c*

(*e*) ANEMIA Anemia is a frequent complication of the infiltration of bone marrow by plasma cells and is usually myelophthisic (*Syllabus*, Unit 14, p 181).

21. PLATE XIV. INFECTIOUS MONONUCLEOSIS

1. *DESCRIPTION OF UPPER PICTURE* The first impression when looking at a blood film like that shown in the upper picture is that of a lymphocytosis On more careful study, it becomes a question whether these cells are lymphocytes or monocytes, for they have many abnormal features The predominating cell is an abnormal or atypical lymphocyte (*4*) showing the following characteristics large size, being as large as or larger than the monocyte (*3*) shown in the same field, irregular shape of the cytoplasm, irregular shape of the nucleus, and clear-blue cytoplasm which varies in intensity of staining The periphery appears deeper blue than other areas, as if the cytoplasm were compressed There may be red or purple granules present in the cytoplasm, but these are scattered and not "peppered" through the cytoplasm, as in the normal monocyte (*3*) In the atypical lymphocytes, the chromatin of the nucleus is not so condensed as in the small lymphocyte, but there may be aggregations of chromatin around the edge or in clumps through the nucleus The chromatin is less condensed than in the small lymphocyte (*2*), but is not as lacy or reticular in structure as in the monocyte The atypical lymphocytes apparently are more fragile than normal white cells and may appear as fragmented forms in fixed preparations The group of atypical lymphocytes in the upper drawing corresponds to the Type II described by Downey [57] and to those illustrated in the report of Baldridge Rohner, and Hansmann [5]

The red cells and platelets in this film are normal

2 *DESCRIPTION OF LOWER PICTURE* The blood film represented here is a real problem in diagnosis, because practically all the white cells are abnormal A careful study shows that there is one normal small lymphocyte (*2*) and a blast form (*7*) with fine granular chromatin structure of the nucleus and deep-blue cytoplasm The fact that most of the cells are immature as indicated by their deep-blue cytoplasm, makes classification more difficult From the characteristics of these cells alone differentiation between the monocytic series and lymphocytic series cannot be made with certainty In fact, these cells are similar to some histiocytes and may be histiocytes from lymphatic tissue However, the occurrence of immature forms (*6*) together with the cells containing vacuolated cytoplasm (*5*) suggests hyperplasia of lymphoid tissue due to infectious mononucleosis These abnormal young forms, which usually are called immature atypical lymphocytes, are similar to those described by Downey as Type III and the vacuolated forms correspond to Downey's Type I [57]

Plasma cells (*8*) are also common when there is a lymphoid hyperplasia The plasma cell shown here is also atypical in that the nucleus is not eccentric

The platelets appear to be normal and the red cells show slight variation in size.

3 *INTERPRETATION OF BOTH PICTURES*

(*a*) MORPHOLOGY OF WHITE CELLS IN INFECTIOUS MONONUCLEOSIS The blood pictures represented here are from two different patients with infectious mononucleosis These changes are also seen in different stages of the disease in the same patient It is difficult, however, to correlate the degree of immaturity of the white cells seen in the blood film with the severity of the illness of the patient or with the phase of disease The pictures are characterized by pathologic mononuclear cells that do not conform to normal stages in development of either the monocytic or the lymphocytic series The study of these cells by means of supravital technique [74, 108 184] has led to the conclusion that they belong to the lymphocytic series Some of the immature forms have nucleoli, but the nucleus is more irregular in shape and the chromatin is more clumped than in the typical lymphoblasts The cells in this plate should be carefully compared with those of plates XI, XII, and XIII to appreciate the abnormal features of these cells

The review by Bernstein [12] gives many important facts about the course of the disease These abnormal cells may exist early in the disease, but typically appear

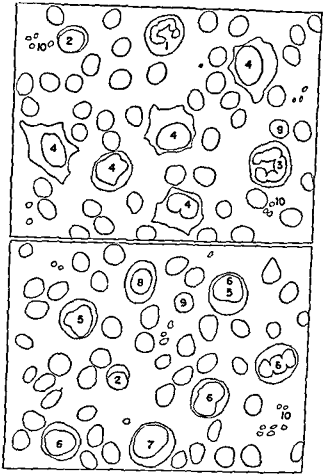


PLATE XIV. INFECTIOUS MONONUCLEOSIS

Key:

1. Neutrophil, band
2. Small lymphocyte
3. Monocyte
4. Atypical lymphocyte, irregular type
5. *Atypical lymphocyte, vacuolated type*
6. Atypical lymphocyte, young type
7. Blast form, probably lymphoblast
8. Plasma cell
9. Normal red cell
10. Platelets

within the first four or five days of illness and rapidly reach a maximum *within a week or ten days The proportion* of "mononuclear" atypical lymphocytes in the cases studied varied from 40 to 90 percent Some of these abnormal forms may persist for nine or ten months after the patient has recovered from clinical signs of the disease

(*b*) WHITE-CELL COUNT The white-cell count may show a marked leukopenia during the first week, but a leukocytosis characterized by atypical and normal *lymphocytes is the rule In 65 cases studied, Bernstein* found 86 percent of the white-cell counts were between 8 0 and $20 \times 10^3/mm^3$ [*12*] In a few instances, the white-cell counts exceeded $40\,0 \times 10^3/mm^3$

(*c*) FORMS OF WHITE CELLS OTHER THAN ATYPICAL LYMPHOCYTES The changes in the blood picture should be followed during the course of the disease, as in all infections The number of eosinophils is decreased during the acute phase, as in many infections, but increases during convalescence Myelocytes may be present in patients who are severely ill The neutrophils are characterized by immature forms (bands), often with toxic granulation

(*d*) RED CELLS AND PLATELETS It is important to *emphasize that the red cells in uncomplicated infectious* mononucleosis are normal This is in contrast to the frequent occurrence of anemia as a complication of leukemia However, the blood picture of infectious mononucleosis may be superimposed on that of any other condition, including diseases involving red cells, such as hypochromic anemia, hemolytic jaundice, anemia due to hemorrhage, or dietary deficiency Stippled cells have been seen in some cases

*The platelets are usually normal in infectious mono-*nucleosis However, a few cases with thrombocytopenia have been reported [*12*]

(*e*) HETEROPHILE ANTIBODY. The Paul-Bunnell test for heterophile antibody is positive in most cases of infectious mononucleosis at some time during the course of the disease The heterophile antibody in this disease is not absorbed by guinea-pig kidney, a test that is highly specific for infectious mononucleosis (*Syllabus, Unit 24, p 380*)

(*f*) GENERAL FEATURES OF INFECTIOUS MONONUCLEOSIS Infectious mononucleosis may be associated with abnormalities of almost any system or organ, thus

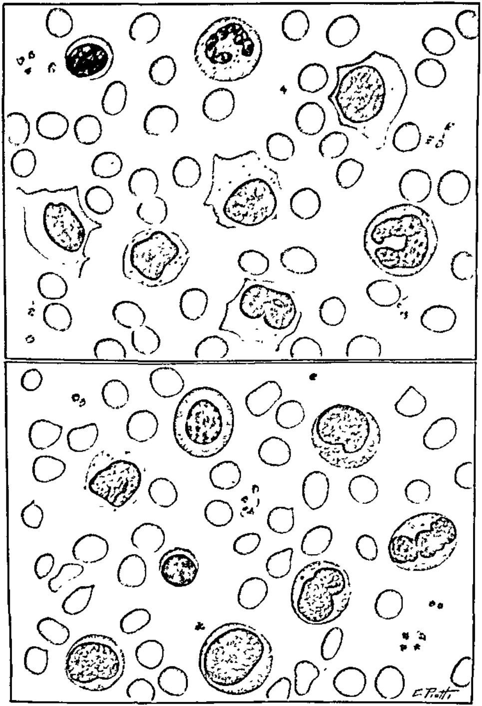


PLATE XIV. INFECTIOUS MONONUCLEOSIS

giving protean manifestations. The outstanding features of "glandular fever" are fever, lymphadenopathy, sore throat, malaise, headache, and gastro-intestinal symptoms There is usually a mild or moderate degree of *hepatitis*

(*g*) DIFFERENTIATION FROM LEUKEMIA Infectious mononucleosis is often diagnosed as leukemia, because of the bizarre forms and immaturity of the white blood cells In the leukemias, however, anemia and thrombocytopenia usually are evident by the time the patient seeks medical attention The heterophile test is uniformly negative in leukemia. In infectious mononucleosis, anemia and thrombocytopenia are not characteristic features of the disease The differentiation of the cell types has been discussed here and in the description of Plate XII.

(*h*) ATYPICAL LYMPHOCYTES IN CONDITIONS OTHER THAN INFECTIOUS MONONUCLEOSIS Atypical lymphocytes similar to the varieties seen in infectious mononucleosis are seen in a number of other conditions In some cases the clinical features of the illness are sufficient to make a differential diagnosis, in some the use of the heterophile test with differential absorption of the antibodies is necessary to differentiate infectious mononucleosis from conditions giving a similar blood picture Young lymphocytes and all stages of plasma cells may be seen in increased numbers in many of these conditions in which the atypical lymphocytes appear

Infectious hepatitis An excellent description of the abnormal lymphocytes in infectious (epidemic) jaundice is reported by Minot and Jones [125] and has been confirmed by more recent studies [6, 86] Although the white-cell count is seldom above normal and often shows leukopenia [171], there is a relative lymphocytosis which frequently shows atypical lymphocytes, young lymphocytes, and cells of the plasmacytic series The heterophile test in infectious (epidemic) hepatitis is *uniformly negative This is of importance* because most patients with infectious mononucleosis have hepatitis which may not be demonstrable clinically but is occasionally associated with jaundice (*Syllabus*, Unit 15, p 206)

Serum sickness The abnormal lymphocytes in serum sickness may be indistinguishable from those of infectious mononucleosis The atypical forms include irregularly shaped, vacuolated, and immature lymphocytes which may constitute as many as 10 percent of the white cells Plasma cells of all stages also appear in increased numbers The unabsorbed serum may show a high concentration of heterophile antibody However, the heterophile antibody (Forssman antibody) of serum sickness is completely absorbed by guinea-pig kidney, which does not remove the heterophile antibody of infectious mononucleosis (*Syllabus*, Unit 24, p 380)

Chicken pox In an excellent study of the blood picture *in 56 patients with varicella, Holbrook [94] has shown* that there is an increase of lymphocytes during the leukopenic phase of the disease During this stage there is an increase of young lymphocytes, lymphoblasts, and abnormal forms, some showing mitotic figures An increase in plasma cells also occurred in 50 percent of the cases, to levels as high as 6 or 8 percent in some instances In another study [37], a case has been observed with the following percentages of cells in the differential count lymphocytes, 27; young lymphocytes, 17, irregular lymphocytes, 5, vacuolated lymphocytes, 2; and *in addition, cells of the plasmacytic series, 7*

Primary atypical pneumonia. A study of the blood picture in 28 cases of virus pneumonia, including 126 white-cell counts, showed that 68 counts (54 percent) were within the normal range (5 to $10 \times 10^3/mm^3$), 5 counts were under $5 \times 10^3/mm^3$ and 53 counts were over $10 \times 10^3/mm^3$ [37] Many of these higher counts occurred during the third and fourth weeks of the disease A greater number of lymphocytes is found early in the disease than is seen in pneumococcus pneumonia There was a slight to moderate increase of young and *irregular lymphocytes, such as is seen in infectious* mononucleosis, during this lymphoid response One patient showed up to 9 percent and another 5 percent of these cells Plasma cells were occasionally seen

Other conditions Abnormal lymphocytes may be present in normal individuals, especially children, in hyperthyroidism, typhoid fever, and infections other than the virus diseases These observations suggest that the appearance of atypical lymphocytes is of no single diagnostic significance but apparently indicates a particular type of response of lymphocytic tissue

(*i*) LYMPHOCYTOSIS AND LEUKEMOID REACTIONS OF LYMPHOCYTIC TYPE Lymphocytosis, either absolute or relative, is seen in many virus infections at some stage in the disease, and in other infectious diseases during the period of recovery The atypical cells, characteristic of infectious mononucleosis, are not usually present

Relative lymphocytosis is the rule in conditions associated with neutropenia, for example, pernicious anemia, *aplastic anemia, agranulocytosis, overwhelming* sepsis, influenza, typhoid fever, typhus fever, malaria, measles, and mumps

Some of the conditions showing an absolute lymphocytosis are *acute infectious lymphocytosis of unknown* etiology [164], thyrotoxicosis [91, 119], German measles (rubella) [112], whooping cough, typhoid fever, and congenital syphilis [5]. Lymphocytosis simulating [illegible] reported in two cases of

the breast with metastasis to lungs and spleen [104]
(A49-60 *)

* Mallory Institute of Pathology

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